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APPLICATION NUMBER

NDA 21-706

Medical Review(s)

**DIVISION OF GASTROINTESTINAL AND COAGULATION
DRUG PRODUCTS**

MEDICAL OFFICER'S REVIEW

NDA: 21-706

Type of Submission: 505 (b)(2)

Sponsor: Santarus, Inc.
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Date Submitted: February 26, 2004

Drug Name: Omeprazole Powder for Suspension 40 mg
(Zegerid™ 40 mg)

Drug Class: Proton-Pump Inhibitor

Proposed Indication: Prevention of Upper Gastrointestinal Bleeding in
Critically Ill Patients
Short-term Treatment of Benign Gastric Ulcer

Documents Reviewed: Clinical section of NDA (electronic submission)
Proposed Label (electronic)
Package Inserts of Prilosec®, Zegerid™, Cimetidine
Electronically Submitted Data Sets

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Clinical Review for NDA 21-706

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Omeprazole Sodium Bicarbonate-Immediate Release (OSB-IR) Powder for Oral Suspension (Zegerid™) 40 mg is recommended to be approvable by this medical officer for the following indications:

- Short-term Treatment of Benign Gastric Ulcer
- Reduction of Risk of Upper Gastrointestinal Bleeding in Critically Ill Patients

Zegerid™ 40 mg should be taken at least one hour before meals after emptying the contents of packet into a small cup containing 20 mL of water. It is for adult use only; there are no adequate and well-controlled studies in pediatric patients for omeprazole containing sodium bicarbonate.

If the suspension is to be administered through a nasogastric or orogastric tube, it should be constituted with approximately 20 mL of water and an appropriately-sized syringe should be used to administer the suspension into the tube, followed by a 20 mL water wash of the tubing.

To get approval, the sponsor should incorporate the labeling recommendations listed in the Medical Officer's Labeling Review (see Appendix B) and the NDA Team's labeling recommendations.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

This Medical Officer recommends that the sponsor conduct a clinical outcome study that will supply information on the benefit of this drug in critically ill pediatric patients. The study can be an open-label, historical control trial. A PK/PD study to determine the appropriate dose in this population is recommended prior to initiating the clinical outcome study.

No Risk Management steps are recommended by this Medical Officer in this submission.

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II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Omeprazole (Prilosec®) is a proton-pump inhibitor (PPI) which has been approved in the United States since 1989. It suppresses gastric acid secretion by specific inhibition of the H⁺/K⁺ adenosine triphosphatase (ATPase) enzyme system at the secretory surface of the gastric parietal cell therefore blocking the final step of acid production. It is currently used for the treatment of acid-related gastrointestinal disorders such as short-term treatment of active duodenal ulcer, gastric ulcer, gastroesophageal reflux disease (GERD), maintenance treatment of healing of erosive esophagitis (EE), treatment of pathological hypersecretory conditions and H. pylori eradication (when used with clarithromycin and/or amoxicillin). It is also approved in children two years and older for the treatment of GERD and other acid-related disorders. It is currently available by prescription as 10 mg, 20 mg, and 40 mg *delayed release capsules*. It is also available over-the-counter (OTC) as a 20 mg omeprazole magnesium (Prilosec® OTC) *delayed release tablet* indicated for the treatment of frequent heartburn.

On June 15, 2004, omeprazole sodium bicarbonate-immediate release (OSB-IR) (Zegerid™20 mg) was approved for the short-term treatment of active duodenal ulcer, GERD, and maintenance of healing EE. Unlike the previously approved delayed release formulations that are delivered with enteric-coating as a protection from rapid degradation upon exposure to acid, this recently approved powder formulation contains 20 mEq sodium bicarbonate as an excipient that replaces the enteric coating and its primary role is to neutralize gastric acid and protect omeprazole from gastric acid degradation until it can be absorbed.

In this submission, the sponsor seeks the approval of Zegerid 40 mg for the short-term treatment (4-8 weeks) of active benign gastric ulcer and for the [] of upper gastrointestinal (UGI) bleeding in critically ill patients. This reviewer feels that the use of the wording "reduction of risk" of UGI bleeding in place of [] is more appropriate in this review.

Zegerid 40 mg contains 40 mg omeprazole and 20mEq sodium bicarbonate as an excipient (the same amount of sodium bicarbonate as the Zegerid 20 mg dose). The sponsor relies on FDA's previous finding of safety and efficacy for omeprazole for the approval of Zegerid 40 mg and submits this NDA under a 505(b)(2) application.

To support the claim for treatment of benign gastric ulcer, Santarus is submitting a bioequivalence study (OSB-IR C02) showing PK and PD profiles for Zegerid 40 mg and Prilosec® 40mg. See Medical Officer's Review of this study (NDA 21-636) dated 5-11-04. By showing that Zegerid and Prilosec (40 mg) have equivalent AUCs and PD effects, the data from the PK/PD trials provide a bridge from Zegerid to the

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Agency's previous findings of safety and efficacy for Prilosec in the treatment of active benign gastric ulcer.

The sponsor is also seeking for the indication of [reduction of risk] of upper GI bleeding in critically ill patients, upper GI bleeding is a clinically important complication in patients who are critically ill. Review of literature shows that almost all critically ill patients develop superficial erosions of the gastric mucosa [or stress related mucosal disease (SRMD)] within 18-24 hours after admission to an intensive care unit; some of these erosions extend into the underlying blood vessels and produce upper gastrointestinal (UGI) hemorrhage. The role of gastric acidity in UGI bleeding is supported by the evidence that inhibiting gastric acid secretion with parenteral administration of an H₂ receptor antagonist, cimetidine can reduce the incidence of bleeding.¹ The basis for SRMD appears to be the inability of the gastric mucosal barrier to provide protection against acid and pepsin in the face of mucosal ischemia.² Clinically significant bleeding from SRMD is associated with increased morbidity, lengthened ICU stay (and cost) by as much as 11 days and mortality rates >50%.³

The reduction of risk of UGI bleeding in critically ill patients will be a new indication for omeprazole. The sponsor supported this indication by submitting study OSB-IRC03 (primary study), a multicenter, triple-blind, Phase 3 study comparing Zegerid to continuous intravenous (IV) cimetidine, the only FDA approved medication for the prevention of UGI bleeding in critically ill patients and other confirmatory evidence, including the PD data from the OSB-IR-C02 trial and literature reports.

In addition, as requested by the Agency, an open-label 8-week safety trial of Zegerid 40 mg in patients with acid-related conditions was added to the clinical program (OSB-IR-C07) due to the Agency's concern about the potential safety issues relating to the higher C_{max} of Zegerid 40 mg compared to Prilosec 40mg delayed release capsules. The upper boundary of the confidence interval around the mean ratio of Zegerid to Prilosec was 133%, exceeding the bioequivalence standard of 125%.

B. Efficacy

The indication for reduction of risk of UGI bleeding in critically ill patients is a new indication for omeprazole or any proton-pump inhibitor. The sponsor conducted OSB-IRC05 in healthy subjects, an open-label, single-period trial to assess the

¹ L. Martin, et al. *Critical Care Medicine*, 1993, Vol.12, No 1, pp 19-30

² J. Reilly and B. Fennerty. *Journal of Pharm Prac*, Dec1998, pp 418-436.

³ R. Jung and R. Maclaren. *Annals of Pharmacotherapy*, Dec2002, pp 1929-1937.

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pharmacokinetics and safety of the Zegerid 40 mg loading dose regimen (given 6-8 hours apart). This loading dose regimen was used in the Phase 3 trial of Zegerid 40 mg in the reduction of risk of UGI bleeding in critically ill patients (OSB-IRC03). OSB-IRC05 demonstrated that when a second 40-mg dose of Zegerid was administered 6 hours after the first dose, there was a 2-fold increase in the bioavailability of omeprazole similar to the 2-fold increase in bioavailability observed after 7 days of repeated daily dosing with Zegerid (and Prilosec) in the OSB-IRC02 trial. Mean AUC(0-inf) after the first dose was 1665, mean AUC(0-inf) after the second dose was 3356.

A single study, OSB-IR C03, a triple-blind, double-dummy, prospective, multicenter, randomized trial which enrolled 359 patients at 46 sites was reviewed to evaluate the efficacy of Zegerid oral powder for suspension for the reduction of risk of UGI bleeding in critically ill patients. Zegerid was compared to continuous intravenous cimetidine, the only FDA approved drug in the prevention of UGI bleeding. The trial assessed the presence of macroscopic bleeding and measured gastric pH of gastric aspirates in patients. The primary efficacy endpoint of this trial was the occurrence of clinically significant UGI bleeding defined as:

On Day 1 and Day 2 of treatment:

- Bright red blood per NG or OG tube that did not clear after NG or OG tube adjustment and 5 to 10 minutes of lavage with room temperature normal saline, or
- Persistent Gastrocult®-positive coffee-ground material for at least eight consecutive hours that did not clear with at least 100 mL of lavage with room temperature normal saline.

On Day 3 through Day 14 of treatment:

- Bright red blood per NG or OG tube that did not clear after NG or OG tube adjustment and 5 to 10 minutes of lavage with room temperature normal saline, or
- Persistent Gastrocult-positive coffee-ground material in at least three consecutive gastric aspirates within 2 to 4 hours (at least 60 ± 20 minutes apart), not clearing with at least 100 mL of lavage with room temperature normal saline.

The protocol design for OSB-IR C03 was similar to the design of the placebo-controlled cimetidine pivotal trial used for the regulatory approval of IV cimetidine for the prevention of UGI bleeding in critically ill patients. The trial design were similar with respect to the dosing schedule for cimetidine, gastric pH criteria for increasing the cimetidine dose, schedule of gastric aspirate assessments, and definition of the primary efficacy endpoint, "clinically significant UGI bleeding". The following were additionally required in the OSB-IR C03 trial: 1) patients were to be mechanically ventilated and have at least one additional risk factor for UGI bleeding, 2) have an APACHE II score > 11 immediately before randomization, 3) enteral feeding was allowed since current medical practice dictates that critically ill patients are to be fed enterally as soon as possible.

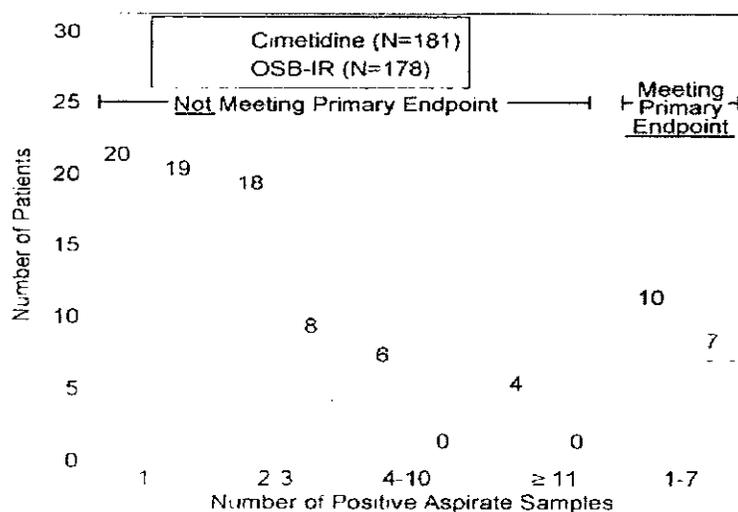
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The results of the study has shown that in the per-protocol population, 10 (6.8%) patients in the cimetidine treatment group and 7 (4.5%) patients in the Zegerid treatment group experienced clinically significant UGI bleeding that meets the primary efficacy endpoint of the trial. Analysis in both per-protocol (PP) and intention to treat (ITT) populations showed that Zegerid 40mg was not inferior to cimetidine with respect to the reduction of risk of clinically significant bleeding; a non-inferiority analysis conducted on the PP population of patients at one-sided $\alpha=0.025$ level of significance, with a similar analysis also conducted on the ITT population of patients. In addition to these 17 patients who met the primary endpoint, 2 patients in the cimetidine group and 1 patient in the Zegerid group were withdrawn from the trial due to clinically meaningful UGI bleeding. Another patient in the cimetidine group was actively bleeding and was transferred to another hospital before the endpoint requirements were met.

There were a total of 75 patients not meeting the primary endpoint (48 for cimetidine, 27 for Zegerid) who had at least one gastric aspirate sample that was positive for UGI bleeding during the trial. Six patients in the cimetidine group had more than 3 positive gastric aspirate samples, none in the Zegerid group; 8 of the Zegerid treated patients had two to three positive gastric aspirate samples, compared to 18 in the cimetidine group. See figure 1. When all patients with any evidence of bleeding were combined, fewer Zegerid treated patients had at least one gastric aspirate containing blood compared to cimetidine-treated patients (34 patients [19.1%] versus 58 patients [32%], respectively; $p=0.005$). These results are supportive of the primary efficacy endpoint outcome that Zegerid is as efficacious as IV cimetidine in reducing the risk of UGI bleeding in critically ill patients.

Figure 1: Number of Patients With Positive Gastric Aspirate Samples



Adapted from sponsor's electronic submission (03) p 61

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Note: A positive gastric aspirate is a gastric aspirate sample that indicated the presence of bright red blood or coffee ground material. Positive gastric aspirates could have occurred on any trial day.

This trial has also shown that the median gastric pH values for patients in the Zegerid group were consistently higher throughout the 14-day trial period compared to those in the cimetidine group. Median daily gastric pH was markedly less variable in the Zegerid group than in the cimetidine group on each of the 14 trial days. There were more patients in the cimetidine group who had one or more occurrences of two consecutive pH measurements ≤ 4 during the trial compared with the Zegerid group ($p < 0.001$). Fewer patients in the Zegerid group required dose increases to keep the gastric pH above 4 (14.6% in the Zegerid group vs. 52.5% in the cimetidine group). It is believed that maintaining gastric pH above 4 decreases the potential for UGI bleeding and prevent progression of mucosal damage.

A bioequivalence study (OSB-IR C02) comparing Prilosec® 40 mg delayed release capsules and Zegerid 40 mg was also conducted to support the indications: treatment of benign gastric ulcer and reduction of risk of UGI bleeding. This trial showed that Zegerid 40mg and Prilosec® 40 mg were found to be bioequivalent with regard to AUC(0-inf) and percent decrease from baseline in integrated gastric acidity over 24 hours on Day 1 and Day 7 of dosing. The Cmax of Zegerid mg was higher than that of Prilosec® which can be explained by the immediate release nature of the formulation. The upper boundary of the confidence interval around the mean ratio of Zegerid to Prilosec was 133%, exceeding the bioequivalence standard of 125%.

C. Safety

Omeprazole has been proven safe and effective in the U.S. for almost 15 years even at high doses (up to 120 mg three times a day); a 20mg omeprazole tablet is available for OTC use. It has been marketed worldwide since 1988 and over 1 billion prescriptions has been written worldwide making it as one of the most frequently prescribed medications.

The sponsor conducted OSB-IR C07 an 8-week, open-label trial to assess the safety of Zegerid 40 mg administered daily to patients with acid-related conditions. Safety data was collected from patients with gastric ulcer, duodenal ulcer, erosive esophagitis, and GERD dosed with Zegerid 40 mg daily for eight weeks. A total of 243 patients were enrolled in the trial and more than 200 patients completed 8 weeks of treatment. Safety was assessed through the evaluation of physical examinations, clinical laboratory assessments, and adverse events. The most frequently reported AEs (among those AEs that occurred in $\geq 1\%$ of patients) included upper respiratory tract infection (15 patients, 6.2%), diarrhea (11, 4.5%), nausea (10, 4.1%), and headache (10, 4.1%). Zegerid 40 mg was well tolerated by patients in this study and the safety profile of Zegerid 40 mg was similar to that described in the Prilosec® labeling.

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In the critically ill patient population (OSB-IR C03), most of the patients in both the Zegerid and cimetidine groups had at least one AE. Drug-related AEs were reported by the investigator for 5 patients in the Zegerid group: nausea (1 patient), rash (2) and pyrexia (1) and hypotension (1). All these are listed in the Prilosec label except for hypotension. A total of 115 patients (32.0%) experienced at least one SAE; 61 patients in the Zegerid group and 54 patients in the cimetidine group. These serious adverse events were all anticipated given the serious underlying disease in these patient population and reflected the severity of the underlying disease states for the patients. There were 48 deaths throughout the trial (Zegerid=27, cimetidine=21); none were considered to be related to trial drug. Four of 17 patients who met the primary endpoint died (2 patients in each group). None of the deaths were directly related to UGI bleeding. It is to be noted that patients in the Zegerid group have higher mean APACHE II score compared to the cimetidine group (24.7 vs. 22.7). Moreover, patients who died in the Zegerid group had a mean APACHE II score of 28 at baseline compared to 24.2 in the cimetidine group, which puts the Zegerid group at higher risk for mortality (~55% vs. ~40%).⁴

Nosocomial pneumonia is a concern in critically ill patients. Drugs used to increase intragastric pH (e.g. antacids, H₂ RAs, PPIs) may increase gastric colonization. The association between stress ulcer prophylaxis and nosocomial pneumonia had been widely debated; however, results of studies that have been conducted to assess this relationship has been inconsistent. The sponsor analyzed this as a separate serious adverse event and the trial (OSB-IRC03) showed no evidence that administration of a daily dose of 40 mg increases the risk of developing nosocomial pneumonia in critically ill patients compared with a continuous IV infusion of cimetidine.

The incidences of death, SAEs, and nosocomial pneumonia were not significantly different for patients in the Zegerid and cimetidine groups during the trial. None of the deaths reported was related to the trial drug. Adverse events and serious adverse events were all related to the underlying disease of patients and severity of their illness.

The combination of postmarketing data, previous clinical trials and adverse events analysis with the studies (OSB-IR C02, C07 & C03) establish the safety of Zegerid. No new omeprazole related safety issues were identified in association with Zegerid treatment of critically ill patients and in patients with acid-related conditions.

Each 40 mg dose packet of Zegerid contains sodium (460mg in the form of sodium bicarbonate); therefore, it should be taken with caution in patients on sodium restricted diet. In addition, this formulation contains 1680mg (20mEq) of sodium bicarbonate; sodium bicarbonate is contraindicated in patients with metabolic alkalosis and hypocalcemia.

⁴ Emergency Medicine at NCEMI On line (www.ncemi.org). APACHE II Score Interpretation

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It should be noted that the more doses of oral omeprazole powder for suspension is given, the more amount of sodium bicarbonate is administered. Each 40mg of omeprazole suspension contains 20 mEq of sodium bicarbonate; therefore, it is possible that in the first 24 hours, a patient could receive a maximum of 60 mEq of sodium bicarbonate.

Sodium Bicarbonate should also be used with caution in patients Bartter's syndrome, hypokalemia, respiratory alkalosis and those with problems with systemic acid-base balance. Further, long-term administration of bicarbonate with calcium or milk can cause milk-alkali syndrome. Known adverse reactions (rate unknown) with sodium bicarbonate include: abdominal pain, flatulence, hypernatremia, metabolic alkalosis, peripheral edema, seizures, tetany, and tremor.

D. Dosing

Dose: Omeprazole Sodium Bicarbonate Powder for Suspension (Zegerid) 40 mg

Indications:

- Reduction of risk of Upper Gastrointestinal Bleeding in Critically Ill Patients
40 mg initially followed by 40 mg after 6 to 8 hours as a loading dose on the first day, then 40mg once daily for up to 14 days
- Short-term Treatment of Benign Gastric Ulcer
40 mg once a day for 4 - 8 weeks

The current package insert for omeprazole states that no dosage adjustment is necessary for the elderly or patients with renal impairment. It also reports that no specific antidote for omeprazole overdosage is known. Treatment should be symptomatic and supportive. Overdosage up to 2400 mg (120 times the usual recommended clinical dose) have been reported. The manifestations included confusion, drowsiness, blurred vision, tachycardia, nausea, vomiting, diaphoresis, flushing, headache, and dry mouth. Symptoms were transient, and no serious clinical outcome has been reported when omeprazole was taken alone.

There was no data provided in this submission regarding dosage adjustment for omeprazole containing sodium bicarbonate; however, due to the sodium and bicarbonate content of Zegerid, caution should be used in patients who require fluid restriction, and those with problems with systemic acid-base balance. Overdose with sodium bicarbonate include hypocalcemia, hypokalemia, hypernatremia, and seizures.

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E. Special Populations

There are no new data regarding the effects of gender, race or age on safety or efficacy. The sponsor refers to the information in the current labeling of Prilosec®.

Pediatric

Pediatric patients were not evaluated in this NDA. No data were submitted by the sponsor regarding this population.

Geriatric

No new data for this new omeprazole formulation containing sodium bicarbonate were submitted by the sponsor regarding this population.

For omeprazole, no dosage adjustment is necessary in the elderly. Pharmacokinetic studies have shown the elimination rate in the elderly was somewhat decreased and bioavailability was increased. The plasma clearance of omeprazole was about half that of young volunteers and its plasma half-life was about twice that of young healthy volunteers. In clinical trials in the US and Europe, omeprazole was administered to over 2000 elderly individuals ≥ 65 years old. No differences in safety and effectiveness between the elderly and younger subjects were noted.

Chronic Hepatic Disease

In patients with chronic hepatic disease, the bioavailability of omeprazole increased to approximately 100% compared to an I.V. dose, reflecting decreased first-pass effect. The plasma half-life of the drug increased to nearly 3 hours compared to the half-life in normal subjects; plasma clearance decreased.

No new data for this new omeprazole formulation containing sodium bicarbonate were submitted by the sponsor regarding this population.

Chronic Renal Impairment

In patients with chronic renal impairment (creatinine clearance of 10-62 mL/min/1.73 m²) the disposition of omeprazole was very similar to that in healthy volunteers, with only a slight increase in bioavailability. Because urinary excretion is a primary route of excretion of omeprazole metabolites, their elimination slowed in proportion to the decreased creatinine clearance.

No new data for this new omeprazole formulation containing sodium bicarbonate were submitted by the sponsor regarding this population. No specific guidelines for sodium bicarbonate dosage adjustment is available in patients with renal impairment.

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Race

In Asians, PK studies of single 20 mg omeprazole doses showed an approximately four-fold increase in AUC when compared to Caucasians. Dose adjustment in Asian subjects should be considered for maintenance of healing of erosive esophagitis.

No new data for this new omeprazole formulation containing sodium bicarbonate were submitted by the sponsor regarding this population.

Pregnancy Use

This application has no new information regarding pregnant women. Omeprazole and sodium bicarbonate are both currently listed as Pregnancy Category C. There are no adequate or well-controlled studies in pregnant women. This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Caution is advised in regular use of sodium bicarbonate in pregnancy. Increased sodium intake during pregnancy can produce edema and weight increase.

Nursing Mothers

Omeprazole concentrations have been measured in breast milk of a woman following oral administration of 20 mg. The peak concentration of omeprazole in breast milk was less than 7% of the peak serum concentration. This concentration would correspond to 0.004 mg of omeprazole in 200mL of milk. Because omeprazole is excreted in human milk, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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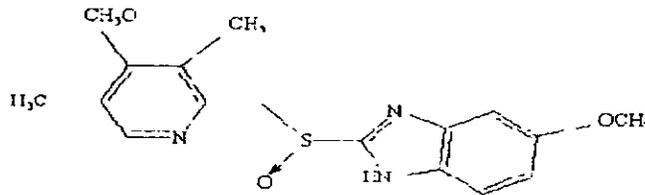
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Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Drug: Omeprazole Sodium Bicarbonate-Immediate Release Powder for Oral Suspension (Zegerid) 40mg



Class: Proton-pump Inhibitor

Proposed Indications:

- Treatment of Upper Gastrointestinal Bleeding in Critically Ill Patients
40mg initially followed by 40mg after 6 to 8 hours as a loading dose on the first day, the 40mg once daily
- Short-term Treatment of Benign Gastric Ulcer
40 mg once a day for 4 - 8 weeks

Preparation and Administration of Suspension:

- Zegerid 40mg should be taken at least one hour before eating.
- Contents of packet should be emptied into a small cup containing 100 ml of water. Stir well and drink immediately. Refill cup with water and drink.
- If the suspension is to be administered through a nasogastric or orogastric tube, it should be constituted with approximately 20 mL of water and an appropriately-sized syringe should be used to administer the suspension into the tube, followed by a 20 mL water wash of the tubing.

Age Group: Adults

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B. State of Armamentarium for Indication(s)

There are five proton pump inhibitors (omeprazole, esomeprazole, pantoprazole, lansoprazole and rabeprazole) approved for use in the United States. Proton pump inhibitors (PPIs) are unstable at a low pH. The oral dosage forms ("delayed release") are supplied as enteric-coated granules encapsulated in a gelatin shell (omeprazole and lansoprazole) or as enteric-coated tablets (pantoprazole and rabeprazole). The granules dissolve only at an alkaline pH, thus preventing degradation of the drugs by acid in the esophagus and stomach. Lansoprazole is supplied as a delayed-release oral suspension composed of enteric-coated granules.

Omeprazole sodium bicarbonate powder for suspension (Zegerid® 20mg) was approved on June 15, 2004 for the short-term treatment of active duodenal ulcer, GERD, and maintenance of healing erosive esophagitis (the 20 mg indications for omeprazole). In this formulation, the enteric-coating is replaced by 20 mEq sodium bicarbonate as a protection from rapid degradation upon exposure to acid until it can be absorbed. Although the neutralization of gastric acid is a direct pharmacologic action of the antacid, the effect is transient and does not contribute to the therapeutic effect for chronic acid-related conditions that require continuous suppression of gastric acid for several days or longer.

C. Important Milestones in Product Development

Omeprazole was originally approved by the FDA in September 1989 for acute treatment only due to concern regarding long-term use. In December 1994, FDA approved the use of omeprazole for maintenance therapy of healing erosive esophagitis. In April 1996, a 14-day regimen consisting of omeprazole and clarithromycin was approved for the treatment of *H. pylori*-associated duodenal ulcer; a 10-day regimen of omeprazole, amoxicillin, and clarithromycin was approved in June 1998. Generic omeprazole capsules were approved in November, 2001.

In July 2002, the FDA approved its use for children 2 years and older for the treatment of acid-related gastrointestinal diseases, including the treatment of symptomatic GERD and maintenance of healing of erosive esophagitis. A non-prescription omeprazole product was approved on June 20, 2003, Prilosec OTC® is indicated for the short-term treatment of frequent heartburn (2 or more episodes per week).

In 1990, Jeffrey Phillips, PharmD and Michael Metzler, MD from the University of Missouri - Columbia began developing a liquid formulation of omeprazole that could be administered through a NG tube. This formulation consisted of omeprazole 20 mg plus 10 mEq sodium bicarbonate and was referred to as "simplified omeprazole suspension" (SOS).

Dr. Michael Metzler submitted IND 46,656 on November 10, 1994 to conduct an open-label study the using simplified omeprazole suspension (SOS) (omeprazole

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bicarbonate solution) in critically ill, mechanically-ventilated patients, who were at risk for UGI bleeding. In late 1995, Dr. Metzler began studying a flavored SOS (Chocobase) for pediatric GERD. He then subsequently transferred ownership of this IND to Santarus, Inc. on January 31, 2001 for commercial development of simplified omeprazole suspension, and SOS was reformulated as a flavored omeprazole suspension containing omeprazole 20 mg or 40 mg plus 20 mEq sodium bicarbonate. This product is referred to as omeprazole immediate-release (Zegerid) powder for oral suspension.

On October 2001, a meeting was held between the Agency and Santarus, Inc. discussing the clinical development plan for Zegerid powder for suspension. The sponsor proposed their plan to conduct a bioavailability (PK/PD) study comparing Zegerid to the listed drug product, Prilosec® Capsules and their plan to conduct a clinical study comparing Zegerid to intravenous cimetidine to support a new indication for PPIs, reduction of risk of upper gastrointestinal bleeding due to stress-related mucosal damage (SRMD) in critically ill patients.

On August 8, 2003, Santarus, Inc. submitted NDA 21-636 for the approval of Zegerid 20mg powder for suspension as an immediate-release omeprazole formulation that can be administered as a liquid. Zegerid® 20 mg was approved on June 15, 2004 for the short-term treatment of active duodenal ulcer, GERD, and maintenance of healing EE. These are indications using the 20 mg dose of omeprazole.

On February 26, 2004 the sponsor submitted NDA 21-706 for the approval of Zegerid 40 mg powder for suspension (Zegerid 40 mg) for the indication of treatment of benign gastric ulcer (a 40 mg indication for omeprazole) and reduction of risk of UGI bleeding in critically ill patients. The latter is a new indication for omeprazole or any PPI.

D. Other Relevant Information

Omeprazole has been marketed worldwide under various trade names since 1988 and was first approved for marketing in the United States (US) in 1989. It is currently marketed under the trade name of Prilosec® in the US and has an excellent safety profile. Over 1.5 billion prescriptions have been written worldwide making it as one of the most frequently prescribed medications. Recently Zegerid™ 20 mg suspension was approved, this formulation contains 20 mEq sodium bicarbonate (1680 mg) as an excipient.

E. Important Issues with Pharmacologically Related Agents

Proton pump inhibitors (PPIs) inhibit the activity of some hepatic cytochrome P450 enzymes and therefore may decrease the clearance of benzodiazepines, warfarin, phenytoin, and many other drugs. A class labeling for PPIs has been recently incorporated in the label regarding potential drug interactions with these

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drugs. The label also includes a statement regarding been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin concomitantly.

When disulfiram is coadministered with a protein pump inhibitor, toxicity has been reported. The most common adverse effects caused by PPIs are nausea, abdominal pain, constipation, flatulence, and diarrhea. Also reported are subacute myopathy, arthralgias, headaches, and skin rashes. There are conflicting data on the risk and clinical implications of enterochromaffin-like cell hyperplasia in patients on long-term proton pump inhibitor therapy. PPIs have a track record of more than 15 years of use worldwide, and no major new issues regarding safety have emerged. There is as yet no reason to believe, therefore, that hypergastrinemia should be a trigger for discontinuation of therapy or that gastrin levels should be monitored routinely in patients on long-term proton pump inhibitor therapy. However, the development of a hypergastrinemic state may predispose the patient to rebound hypersecretion of gastric acid following discontinuation of therapy.⁵

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

No new animal or toxicology studies were submitted with this NDA. In the most recent package insert of omeprazole, animal studies in a two 24-month carcinogenicity studies in rats, omeprazole at daily doses of about 0.7 to 57 times human dose produced gastric ECL cell carcinoids in a dose-related manner. An increased incidence of ECL cell hyperplasia was observed in the treated group when compared to the control group over a two-year period. Gastric adenocarcinoma was seen in one rat (2%); this finding involving only one tumor is difficult to interpret. A 26-week p53 (+/-) transgenic mouse carcinogenicity study was not positive. See Pharm/Tox review.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

A Comparison of the PK/PD of Zegerid 40 mg suspension and Prilosec® 40 mg Delayed-Release Capsules in Healthy Subjects (OSB-IR C02) showed that after one dose (day 1), Zegerid 40 mg and Prilosec 40 mg were bioequivalent with respect to AUC but not to C_{max}. The least-squares mean ratio for Zegerid to Prilosec was 87.9% for AUC(0-inf) with the boundaries of the 90% CI within 80% and 125% compared with Prilosec. The C_{max} for Zegerid 40 mg was higher than for Prilosec 40 mg (mean ratio 151.10%, 90% CI of

⁵ GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS - 10th Ed (2001) Online

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124.02% to 184.09%). The T_{max} value for Zegerid was shorter (0.44 hr) than the T_{max} value for Prilosec (2.34 hr) ($p < 0.001$).

On day 7 (at steady state), Zegerid 40 mg and Prilosec 40 mg administered once a day in the morning were bioequivalent with respect to AUC (0-inf); the least-squares means ratio was 101.91% with a 90% CI of 95.25% to 109.02%. The C_{max} for Zegerid 40 mg at steady state was slightly higher than for Prilosec (mean ratio of 119.50%, 90% CI of 107.23% to 133.17 %). The T_{max} value for the immediate-release product was shorter (0.58 hr) than the T_{max} value for Prilosec (1.77 hr) ($p < 0.001$).

Administration of Zegerid 40mg one hour postmeal reduced the bioavailability to 72.82% [percent mean ratio (postmeal:premeal) for AUC(0-inf)] of the premeal value. Administration after the meal lowered the C_{max} mean ratio (postmeal:premeal) to 40.25% and delayed the mean T_{max} by 0.92 hours (55 minutes).

OSB-IR C05 is a PK trial conducted in healthy subjects to determine the Zegerid loading dose regimen that will be used for the reduction of risk of UGI bleeding in critically ill patients. This study demonstrated that when a second 40-mg dose of Zegerid was administered 6 hours after the first dose, there was a 2-fold increase in the bioavailability of omeprazole similar to the 2-fold increase in bioavailability observed after 7 days of repeated daily dosing with Zegerid (and Prilosec) in the OSB-IRC02 trial. Mean AUC(0-inf) after the first dose was 1665, Mean AUC(0-inf) after the second dose was 3356. Also refer to Biopharm Review, Nov. 2004.

B. Pharmacodynamics

Study results of OSB-IR C02 have demonstrated that all four PD parameters (integrated acidity, mean gastric acid concentration, percent time gastric pH <4, and median gastric pH) indicated that gastric acid suppression occurred after one dose and subsequently greater after the seventh dose for both treatments. The median percent time gastric pH was less than or equal to 4 was somewhat higher on Day 1 for Zegerid (53%) than for Prilosec (43%), but were the same on Day 7. Each of the four gastric acid parameters showed similar levels of suppression for the two omeprazole formulations.

In study OSB-IR C03, pH of gastric aspirates was measured at regular intervals throughout the trial to evaluate the effectiveness of treatment. Median daily gastric pH in the Zegerid 40 mg group was significantly higher compared to the IV cimetidine group for each of the 14 days of the study, and fewer patients required dose increases to keep the gastric pH above 4. Median daily gastric pH was less variable in the Zegerid group for each of the 14 trial days than that in the cimetidine group. Loss of previously adequate pH control was observed more often in the cimetidine group (22.5%) than in the Zegerid group (6.5%) ($p < 0.001$).

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IV. Description of Clinical Data and Sources

A. Overall Data

The sources of data used in the review were based on the sponsor's data from two primary studies: OSB-IR C03, a double-blind, multicenter, randomized, active-control efficacy and safety study in 359 critically ill patients comparing oral Zegerid 40 mg to intravenous cimetidine for up to 14 days; and OSB-IR C02, an open-label bioequivalence study in 32 healthy subjects comparing the PK/PD profiles of Zegerid 40 mg and Prilosec®40 mg. Study OSB-IR C07, an open-label, single-arm, multicenter, safety study in 244 patients with acid-related disorders was also submitted to support this NDA. See table 1. Literature reports for the prevention of upper GI bleeding were also utilized by this medical officer in the review of this NDA.

B. Tables Listing the Clinical Trials

Table 1: Clinical Trials in Support of NDA 21-706

| <i>Type of Trial</i> | <i>Trial Name</i> | <i>Objective</i> | <i>Design</i> | <i>Dosage and Administration</i> | <i>Subjects</i> | <i>Duration of Treatment</i> |
|----------------------|-------------------|---|--|---|-----------------------------|--|
| Primary | | | | | | |
| Efficacy and Safety | OSB-IR-C03 | To demonstrate that Zegerid is efficacious in preventing UGI bleeding | Prospective triple blind, double dummy, MC, rand. w/ active control (cimetidine) | Zegerid 40mg susp, 2 doses 6-8 hrs. apart on Day, then 40mg qd, via NG/OG tube Cimetidine 300mg loading dose on Day 1 the 50mg continuous IV | 359 Critically ill patients | Up to 14 days |
| PK/PD | OSB-IR-C02 | To compare PK/PD profiles of Zegerid and Prilosec | Crossover (Zegerid 40mg vs Prilosec 40mg) | Zegerid 40mg suspension, q.d. 7 days or q.d. 8 days po Prilosec 40mg qAM 7 days, po | 32 Healthy | Zegerid- 7 or 8 days Prilosec- 7 days |
| Supportive | | | | | | |
| PK | OSB-IR-C05 | To define PK profile of Zegerid loading dose regimen | Single arm (no control) | Zegerid 40mg susp, 2 doses 6-8 hrs. apart oral | 12 Healthy | 1 day |
| PK/PD | OSB-IR-C06 | To compare PK/PD profiles of Zegerid and Prilosec | Crossover (Zegerid 20mg vs Prilosec 20mg) | Zegerid 20mg suspension, qd 8 days or qd 7 days and bid 1 day, po Prilosec 20mg q AM 7 days, po | 36 Healthy | Zegerid- 8 days, Prilosec- 7 days |

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| | | | | | | |
|--------|-----------|--|--|--------------------------------------|--|---------|
| Safety | OSB-IRC07 | To assess the safety profile of Zegerid in patients w/ acid-related diseases | Open-label, single arm, prospective, multicenter | Zegerid 40 mg once daily for 8 weeks | 244 Patients w/ acid-related disorders | 8 weeks |
|--------|-----------|--|--|--------------------------------------|--|---------|

C. Postmarketing Experience

Omeprazole has been marketed worldwide under various trade names since 1988 and was first approved for marketing in the United States (US) in 1989. It is currently marketed under the trade name of Prilosec® in the US. Omeprazole is one of the most frequently prescribed medications with over 1.3 prescriptions written worldwide to date. The 20 mg dose is available as an OTC medication for treatment of frequent heartburn. No postmarketing safety issue regarding the use of omeprazole has been identified so far.

Omeprazole Sodium Bicarbonate-Immediate Release Powder for Suspension 20 mg (Zegerid™) has been newly approved for use in the U.S. on June 15, 2004. There is so far no postmarketing safety issue regarding its use has been identified.

D. Literature Review

The sponsor submitted a list of references/articles from peer reviewed journal and published articles. This reviewer has also searched the literature for information on omeprazole and sodium bicarbonate; 1 of UGI bleeding in critically ill patients; and incorporated this information in the review.

V. Clinical Review Methods

A. How the Review was Conducted

The proposal for the use of a higher dose (40 mg) omeprazole sodium bicarbonate powder for suspension for the reduction of risk of UGI bleeding in critically ill patients and treatment of active benign gastric ulcer was based on the comprehensive review of two studies: *OSB-IR C02*: a comparison of the PK/PD of Zegerid 40 mg suspension and Prilosec® 40 mg delayed-release capsules in healthy subjects, and *OSB-IR C03*: a comparison of Zegerid to intravenous cimetidine for the prevention of upper gastrointestinal bleeding in critically ill patients. In addition, an 8-week, open-label, single arm, prospective, multicenter safety study (*OSB-IR C07*) to assess the safety profile of Zegerid in patients with acid-related disorders was also reviewed. In this submission, studies *OSB-IR C03* and *OSB-IR C02* were both reviewed in detail for efficacy and safety, and *OSB-IR C07* was reviewed for safety.

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B. Overview of Materials Consulted in Review

Clinical Section of the NDA Volume 1 paper copy

NDA Electronic Submission

Package Insert for:

- Prilosec®
- Zegerid™
- Cimetidine®

Pharmacology Online

Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 9th ed.
(Online)

Harrison's: Principles of Internal Medicine, 16th ed. (Online)

Haubrich and Schaffner: Gastroenterology, 5th ed.

Drug Information Handbook, 8th ed.

Medical Officer's Review of NDA 21-636

C. Overview of Methods Used to Evaluate Data Quality and Integrity

A comprehensive review of clinical study OSB-IR C03 for the reduction of risk of UGI bleeding in critically ill patients and bioequivalence study OSB-IR C02 comparing the PK/PD of OSB and Prilosec (40 mg) was performed.

A DSI audit conducted in one center for study OSB-IR C03, and the records of 17 out of 50 randomized subjects were reviewed. The field investigator reported the following violations: 1) the Principal Investigator did not promptly report serious adverse events to the sponsor; and 2) there were protocol violations reported, 3 subjects received Pepcid and 2 patients received magnesium hydroxide, both are prohibited medications. It was also reported that gastric pH was not recorded at all protocol specified times for some subjects, the second oral study drug was not administered after Day 1 initial dose for 3 subjects, and oral study drug was not increased for one subject despite the gastric pH being less than 4 on two occasions. These violations, however, would not affect the validity of the data as per the field investigator.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The sponsor states that this research was carried out in accordance with the clinical research guidelines established by the Basic Principles defined in the US 21 Code of Federal Regulations (CFR) Parts 50, 56, and 312 and the principles delineated in the latest version of the Declaration of Helsinki (Hong Kong, September 1989; Somerset West, Republic of South Africa, October 1996; and Edinburgh, Scotland, October 2000).

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E. Evaluation of Financial Disclosure

The applicant submitted an FDA form 3454 certifying that none of the investigators of the covered clinical studies had any financial interests to disclose.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Treatment of Benign Gastric Ulcer

A bioequivalence study, OSB-IR C02, comparing the PK and PD profiles of Zegerid 40 mg and Prilosec at 40 mg dose of omeprazole in healthy subjects is included in this submission to support the indication of treatment of benign gastric ulcer. The results of OSB-IR C02 have shown that Zegerid 40 mg and Prilosec 40mg delayed release capsules were bioequivalent with respect to AUC but not to C_{max}; the upper boundary of the confidence interval around the mean ratio of Zegerid 40 mg to Prilosec 40 mg was 133%, exceeding the bioequivalence standard of 125%. This higher C_{max} for Zegerid can be attributed to the elimination the delayed-release coating, hence the difference in release rates between the two formulations. By showing that Zegerid and Prilosec have equivalent AUCs and PD effects, the OSB-IR C02 trial has provided a bridge from Zegerid to the previous findings of FDA of the safety and efficacy of Prilosec in the treatment of active benign gastric ulcer.

However, ingestion of Zegerid 40 mg an hour after taking a high-fat meal reduced the bioavailability to 72.82% for AUC(0-inf)] of the premeal value. Administration after the meal lowered the C_{max} mean ratio (postmeal:premeal) to 40.25% and delayed the mean T_{max} by 0.92 hour (55 minutes).

Overall, with regards to PD findings, Zegerid 40 mg appears to be comparable with regards to inhibition of acid secretion relative to Prilosec® Delayed Capsules 40mg. The efficacy of Prilosec (omeprazole) is related to its ability to suppress gastric acid; Zegerid 40 mg appears to be comparable to Prilosec 40 mg with regards to inhibition of acid secretion. Therefore, the results of the studies provide an important evidence of Zegerid's therapeutic effect.

Reduction of risk of Upper GI Bleeding in Critically Ill Patients

A pivotal study (OSB-IR C03) that enrolled 359 patients at 46 sites was submitted for the indication of reduction of risk of UGI bleeding in critically ill patients and is supported by a PK/PD study (OSB-IR C02) discussed above. The results of these studies demonstrated that Zegerid is efficacious in preventing UGI bleeding in critically ill patients.

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Study OSB-IR C03 compares the rates of clinically significant UGI bleeding in critically ill patients at risk for SRMD treated with either Zegerid 40 mg or continuous IV cimetidine (the only FDA approved medication for the prevention of UGI bleeding). The primary endpoint was bright red blood per NGT/OGT or persistent Gastrocult®-positive coffee-ground material that did not clear after lavage (see Appendix B for details on endpoints). There were 10 (6.8%) patients in the cimetidine group and 7 (4.5%) patients in the Zegerid group who had clinically significant UGI bleeding and met the primary efficacy endpoint of the trial using PP analysis; in the ITT analysis, 3.9% of patients in the Zegerid group and 5.5% in the cimetidine group met the primary efficacy endpoint. See table 2 below. Results show that Zegerid 40mg once daily after a loading dose was not inferior and as efficacious as continuous IV cimetidine in preventing UGI bleeding in critically ill patients.

Table 2: Number (%) of Patients with Clinically Significant Bleeding by Analysis Population (OSB-IR-C03)

| Analysis Population | OSB-IR n (%) | Cimetidine n (%) | Difference in Bleeding Rates (%) | Confidence Interval for the Difference in Bleeding Rates (%) | P-value* |
|---------------------|-----------------|---------------------|----------------------------------|--|----------|
| Per-Protocol | 7 (4.5) | 10 (6.8) | -2.4 | (-100.0, 2.8) | 0.003 |
| Intent-to-Treat | 7 (3.9) | 10 (5.5) | -1.6 | (-100.0, 2.8) | 0.002 |

From sponsor's electronic submission OSB-IR C03

In addition to the patients meeting the primary endpoint of clinically significant UGI bleeding, there were patients who had evidence of UGI bleeding that did not meet the primary endpoint, but may have been clinically meaningful. The percentage of patients who had UGI bleeding not meeting the primary endpoint was higher in the cimetidine group (N=48, 26.5%) than in the Zegerid group (N=27, 15.2%), p = 0.0094. See table below. These findings are supportive of the primary efficacy endpoint results.

Table 3: Number (%) of Patients With UGI Bleeding That Did Not Meet the Primary Endpoint (OSB-IR-C03)

| BLEEDING | Zegerid (N=178) | Cimetidine (N=181) | P-value* |
|--|--------------------|-----------------------|----------|
| | n (%) | n (%) | |
| UGI bleeding that did not meet primary efficacy endpoint | 27 (15.2) | 48 (26.5) | 0.0094 |
| Discontinued while actively bleeding | 1 (0.6) | 3 (1.7) | |

From sponsor's electronic submission of OSB-IR C03

This trial also assessed gastric pH values and has shown that the median gastric pH for patients in the Zegerid group were consistently higher throughout the 14-day trial period compared to those in the cimetidine group (see table 13A). Median daily gastric

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pH was markedly less variable in the Zegerid group than in the cimetidine group on each of the 14 trial days. There were more patients in the cimetidine group who had one or more occurrences of two consecutive pH measurements ≤ 4 during the trial compared with the Zegerid group (58% vs. 32% , $p < 0.001$). Fewer patients in the Zegerid group required dose increases to keep the gastric pH above 4 (14.6% in the Zegerid group vs. 52.5% in the cimetidine group). It is believed that maintaining gastric pH above 4 decreases the potential for UGI bleeding and prevent progression of mucosal damage.

B. General Approach to Review of the Efficacy of the Drug

Efficacy was assessed by utilizing the data submitted by the applicant comprising a bioequivalence study (OSB-IR C02) and a Phase 3 safety and efficacy study (OSB-IR C03). Studies were reviewed for efficacy results. Statistical analysis were reviewed in consultation with the statistician. Summaries, supporting tables and case reports were reviewed as needed. A literature search was also conducted by this reviewer for published peer reviewed articles on the reduction of risk of UGI bleeding; gastrointestinal and intensive care textbooks were consulted as well.

C. Detailed Review of Trials by Indication

Study OSB-IR C03: See Appendix A

Study OSB-IR C02: See Medical Officer's Review of NDA 21-636, Appendix A

D. Efficacy Conclusions

Reduction of risk of UGI bleeding in critically ill patients is a new indication for omeprazole (or any PPI). A large, multicenter, triple-blind, double-dummy, prospective, randomized trial, study OSB-IR C03, which enrolled 359 patients at 46 sites was reviewed to evaluate the efficacy of Zegerid oral powder for suspension for the reduction of risk of UGI bleeding in critically ill patients. In the per-protocol population, 10 (6.8%) patients in the cimetidine treatment group and 7 (4.5%) patients in the Zegerid treatment group experienced clinically significant UGI bleeding and met the primary efficacy endpoint of the trial, in the ITT analysis, 3.9% of patients in the Zegerid group and 5.5% in the cimetidine group met the primary efficacy endpoint. It has been demonstrated in this study that Zegerid 40 mg was not inferior to cimetidine with respect to the reduction of risk of clinically significant bleeding in critically ill patients in the both PP and ITT populations.

In addition to the 17 patients who met the primary endpoint, 2 patients in the cimetidine group and 1 patient in the Zegerid group were withdrawn from the trial due to clinically meaningful UGI bleeding. Another patient in the cimetidine group was actively bleeding and was transferred to another hospital before the endpoint requirements were met.

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There were a total of 75 patients not meeting the primary endpoint (cimetidine=48, Zegerid=27) who had at least one gastric aspirate sample that was positive for UGI bleeding during the trial. Six patients in the cimetidine group had > 3 positive gastric aspirates samples, none in the Zegerid group; 8 of the Zegerid treated patients had two to three positive gastric aspirate samples, compared to 18 in the cimetidine group. When all patients with any evidence of bleeding were combined, fewer Zegerid treated patients had at least one gastric aspirate containing blood compared to cimetidine-treated patients (34 patients [19.1%] versus 58 patients [32%], respectively; $p=0.005$). This data support the efficacy of Zegerid 40mg in preventing UGI bleeding in critically ill patients.

This trial has also shown that the median gastric pH was markedly less variable in the Zegerid group than in the cimetidine group on each of the 14 trial days. There were more patients in the cimetidine group who had one or more occurrences of two consecutive pH measurements ≤ 4 during the trial compared with the Zegerid group (58% vs. 32% , $p<0.001$).

The protocol design for OSB-IR C03 was similar to the design of the placebo-controlled cimetidine pivotal trials used for the regulatory approval of IV cimetidine for the reduction of risk of UGI bleeding in critically ill patients that included two studies with a total of 218 participants. The trial design were similar with respect to dosing schedule for cimetidine, gastric pH criteria for increasing the cimetidine dose, schedule of gastric aspirate assessments, and definition of the primary efficacy endpoint, "clinically significant UGI bleeding". The following were additionally required in the OSB-IR C03 trial: 1) patients were to be mechanically ventilated and have at least one additional risk factor for UGI bleeding, 2) have an APACHE II score > 11 immediately before randomization, and 3) enteral feeding was allowed since current medical practice dictates that critically ill patients are to be fed enterally as soon as possible.

A study with 359 patients in 46 sites appears to be sufficient when compared to the cimetidine study where a total of 218 patients participated (in two pivotal studies). The results of the OSB-IR C03 has replicated the findings of the cimetidine trial (NDA 17-939, S-077) in the prevention of UGI bleeding in critically patients. The link between reduction in gastric acidity and effectiveness in reduction of risk of UGI bleeding in critically ill patients is also supported by the FDA approval of IV cimetidine (an acid reducer) for this indication as well as by the routine "off-label" use by physicians of other H₂RAs and PPIs (IV pantoprazole and simplified omeprazole suspension by NG/OG tube). H₂RAs and PPIs are known to be effective in suppressing gastric acid and in treating various acid-related conditions. Therefore, there is substantial evidence that if cimetidine is efficacious in preventing UGI bleeding in critically ill patients then a PPI will also provide a similar therapeutic effect.

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A bioequivalence study (OSB-IR C02) comparing Prilosec® 40 mg delayed release capsules and Zegerid 40 mg was also conducted to support reduction of risk of UGI bleeding indication and treatment of benign gastric ulcer indication. This trial showed that Zegerid 40 mg and Prilosec® 40 mg Zegerid were found to be bioequivalent with regard to AUC(0-inf) and percent decrease from baseline in integrated gastric acidity over 24 hours on Day 1 and Day 7 of dosing. The C_{max} of Zegerid mg was higher than that of Prilosec® which can be explained by the immediate release nature of the formulation. The upper boundary of the confidence interval around the mean ratio of Zegerid to Prilosec was 133%, exceeding the bioequivalence standard of 125%. The equivalence in AUC and PD effects provides a bridge from Zegerid to the Agency's previous findings of safety and efficacy for Prilosec in the treatment of active benign gastric ulcer.

The studies have shown that all four PD parameters (integrated acidity, mean gastric acid concentration, percent time gastric pH <4, and median gastric pH) indicated that gastric acid suppression occurred after one dose and greater after the seventh dose for both Zegerid and Prilosec (40 mg). Each of the four gastric acid parameters mentioned above showed similar levels of suppression for the two omeprazole formulations. OSB-IR C02 trial has demonstrated that Zegerid 40 mg and Prilosec 40 mg were comparable in suppressing gastric acid secretion and provide support of therapeutic equivalence for Zegerid 40 mg and Prilosec® 40 mg.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Omeprazole has been marketed worldwide under various trade names since 1988 and in the US since 1989. It is one of the most frequently prescribed medications with over 6 prescriptions written worldwide. The safety experience for Prilosec® has been up to high doses (360 mg per day). Omeprazole 20mg (Prilosec OTC®) has also been approved for over the counter use since June 2003. Zegerid 20 mg (Zegerid™) was approved for use as a prescription drug in June, 2004.

In this submission, the sponsor has demonstrated the safety of Zegerid 40 mg in critically ill patients for use up to 14 days (OSB-IR C03), in those with acid-related disorders for use up to 8 weeks (OSB-IR C07), and in healthy subjects (OSB-IR C02), for use up to 8 days. The safety outcome measures were changes in physical and laboratory examinations, vital signs, adverse events, serious adverse events.

There are no new safety concerns identified in this submission. The data in the OSB-IR C07 8-week safety study conducted in patients with acid-related disorders shows that the safety profile of Zegerid 40 mg is similar to that of Prilosec 40 mg. In the OSB-IR C03 trial conducted in critically ill patients, adverse events reported were similar in both treatment groups and were a reflection of the severity of the patients'

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underlying medical conditions. No new omeprazole-related safety issues were identified in association with Zegerid treatment of critically ill patients.

Further, the trial (OSB-IRC03) showed no evidence that administration of a daily dose of 40 mg increases the risk of developing nosocomial pneumonia in critically ill patients when compared with patients on a continuous IV infusion of cimetidine.

B. Description of Patient Exposure

In the OSB-IR C02 trial, 16 (50%) of the subjects received eight doses of Zegerid 40 mg and 15 (47%) of the subjects received seven doses of Zegerid 40 mg. A total of 31 (97%) subjects received seven doses of Prilosec 40 mg. One subject (# 3), discontinued the trial because of an AE; received seven doses of Prilosec and only six doses of Zegerid. One subject (#6) missed the third dose of Prilosec thus received eight doses of Zegerid and six doses of Prilosec.

In the OSB-IR C03 trial, a total of 359 patients entered the trial and were exposed to the trial drug; 178 patients for Zegerid and 181 for cimetidine. Patients in the Zegerid group received the trial drug for a mean of approximately 6.60 days compared with 7.05 days for patients in the cimetidine group. Approximately 50% of patients in both the Zegerid and cimetidine treatment groups were still being treated with trial drug by Day 6, with approximately 15% of the patients in both groups still in the trial on Day 14. A total of 264 patients (73.5%) completed the trial; 124 (69%) for Zegerid and 140 (77.3%) for cimetidine. See table below for summary of patient disposition.

**Table 4: Summary of Patient Disposition
(OSB-IR C03)**

| | Zegerid (N=178) n (%) | Cimetidine (N=181) n (%) | Total (N=359) n (%) |
|--|-----------------------------|--------------------------------|---------------------------|
| Patients | | | |
| Exposed to trial drug | 178 | 181 | 359 |
| Completed | 124 (69.7) | 140 (77.3) | 264 (73.5) |
| <i>Discontinued due to:</i> | | | |
| Death | 15 (8.4) | 15 (8.3) | 30 (8.4) |
| Abnormal laboratory test result | 5 (2.8) | 5 (2.8) | 10 (2.8) |
| Drug-related AE | 2 (1.1) | 2 (1.1) | 4 (1.1) |
| NG/OG tube removal | 14 (7.9) | 7 (3.9) | 21 (5.8) |
| Administrative | 18 (10.1) | 12 (6.6) | 30 (8.4) |

Adapted from sponsor's electronic submission Trial C03 p 49

The numbers (%) of patients withdrawn from the OSB-IR-C03 trial and the reasons for withdrawal were similar in the Zegerid and cimetidine treatment groups except for NG/OG tube removal. There were more Zegerid treated patients

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who were discontinued due to NG tube removal (7.9% vs. 3.9%) compared to cimetidine treated patients; this may be reflective of the patients improved medical status. Administrative reasons for withdrawal were use of unapproved concomitant medications, withdrawal of consent, noncompliance with protocol, intercurrent illness, injury or medical condition, or the investigator felt withdrawal was justified.

The table below lists in detail the reason for trial completion or discontinuation.

Table 5: Disposition of Patients

| Reason for Trial Completion or Discontinuation | OSB-IR (n=178) | | Cimetidine (n=181) | | Total (n=359) | |
|--|----------------|---------|--------------------|---------|---------------|---------|
| | N | (%) | N | (%) | N | (%) |
| 1) Completion of 14 days of trial drug treatment with no clinically significant upper GI bleeding | 26 | (14.6) | 31 | (17.1) | 57 | (15.9) |
| 2) Discharge from critical/intensive care unit before completing 14 days of trial drug treatment with no clinically significant active upper GI bleeding | 5 | (2.8) | 4 | (2.2) | 9 | (2.5) |
| 3) Ventilatory extubation | 86 | (48.3) | 96 | (53.0) | 182 | (50.7) |
| 4) Development of clinically significant active upper GI bleeding | 7 | (3.9) | 9 | (5.0) | 16 | (4.5) |
| 5) Death | 15 | (8.4) | 15 | (8.3) | 30 | (8.4) |
| 6) Development of any laboratory abnormality(ies) | 5 | (2.8) | 5 | (2.8) | 10 | (2.8) |
| 7) Use of unapproved concomitant medications | 4 | (2.2) | 1 | (0.6) | 5 | (1.4) |
| 8) Occurrence of intolerable AE(s) judged to be related to trial drug | 2 | (1.1) | 2 | (1.1) | 4 | (1.1) |
| 9) Withdrawal of consent by patient or patients legally authorized representative | 4 | (2.2) | 3 | (1.7) | 7 | (1.9) |
| 10) Noncompliance with protocol | 1 | (0.6) | 0 | (0.0) | 1 | (0.3) |
| 11) Development of an intercurrent illness, injury, or medical condition likely to interfere with patient safety, the overall assessment, or the required administration of trial drug | 3 | (1.7) | 1 | (0.6) | 4 | (1.1) |
| 12) Development of any condition for which the investigator feels treatment withdrawal is justified | 2 | (1.1) | 3 | (1.7) | 5 | (1.4) |
| 13) Termination or suspension of the trial by the sponsor or investigator for administrative reasons | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| 14) Other | 18 | (10.1) | 11 | (6.1) | 29 | (8.1) |

Adapted from sponsor's electronic submission Trial C03 Post-Text Table 15.1-2

In the OSB-IR C07 trial, 243 patients were enrolled and exposed to Zegerid 40 mg, with 225 patients (92.6%) completing 8 weeks of treatment. A total of 18 (7.4%) patients discontinued due to: intolerable adverse events (5=2.1%), withdrawal of consent by patient (1=0.4%), noncompliance with protocol (4=1.6%), development of an intercurrent illness that can interfere with patient safety, development of any condition in which treatment withdrawal is felt to be justified (1=0.4%) death (1=0.4), other (3=1.2%).

One of the patients (Patient 09-102) died suddenly approximately one week after starting trial drug. The cause of death was considered to be related to coronary artery disease and not related to the trial drug. Patients who discontinued participation in the trial due to "other" reasons included: one patient who objected to the bitter-sweet taste of the trial drug (Patient 05-173), one patient who was no longer considered an acceptable candidate for the trial by the investigator (Patient 05-268), and one patient who reported lack of efficacy (Patient 06-403).

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C. Methods and Specific Findings of Safety Review

A total of three primary studies were reviewed in this submission. One study was reviewed in this submission to assess the bioequivalence of Zegerid 40mg and Prilosec®40mg, *OSB-IR C02*. The subjects in this trial were healthy volunteers and did not specifically assess safety issues with this formulation of omeprazole. The majority of the AEs reported in the three Zegerid PK/PD trials were rated as mild. See Medical Officer Review of NDA 21-636 Appendix A: *OSB-IR C02*.

The Agency expressed concern about potential safety issues relating to the higher C_{max} of Zegerid 40 mg compared to Prilosec 40 mg delayed release capsules; the upper boundary of the confidence interval around the mean ratio of Zegerid to Prilosec was 133%, exceeding the bioequivalence standard of 125%. The sponsor was requested to perform an 8-week open-label safety trial with Zegerid 40 mg in patients with acid-related conditions to address this issue.

The sponsor conducted *OSB-IR C07* an 8-week, open-label single arm, prospective, multicenter trial to assess the safety of Zegerid 40 mg administered daily to patients with acid-related conditions. Safety data was collected from patients with gastric ulcer, duodenal ulcer, erosive esophagitis, and GERD dosed with Zegerid 40 mg daily for eight weeks. A total of 243 patients were enrolled in the trial and 225 (92.6%) patients completed 8 weeks of treatment. Safety was assessed through the evaluation of physical examinations, clinical laboratory assessments, and adverse events. The most frequently reported AEs (that occurred in $\geq 1\%$ of patients) included upper respiratory tract infection (15 patients, 6.2%), diarrhea (11, 4.5%), nausea (10, 4.1%), and headache (10, 4.1%). Frequently occurring drug-related AEs observed were in the gastrointestinal (abdominal pain, constipation, diarrhea, nausea) and nervous (headache) systems; are included in the Prilosec labeling. The respiratory tract infection NOS or rash NOS AEs were not considered to be related to the trial drug. Zegerid 40 mg was well tolerated by patients in this study and the safety profile of Zegerid 40 mg was similar to that described in the Prilosec® labeling. Table 6 below illustrates frequently occurring adverse events in study *OSB-IR C07* per investigator assessment.

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Table 6: Number and Percent of Patients with Frequently Occurring Adverse Events (experienced by $\geq 3\%$ of patients) by Body System and Preferred Term MedDRA Body System (OSB C07)

| MedDRA Body System Preferred Term | OSB-IR 40 mg (N=243) | | | |
|---|----------------------|-------|------------------|-------|
| | All AEs | | Drug-Related AEs | |
| | n | (%) | n | (%) |
| GASTROINTESTINAL DISORDERS | | | | |
| Abdominal pain NOS | 8 | (3.3) | 3 | (1.2) |
| Constipation | 8 | (3.3) | 3 | (1.2) |
| Diarrhoea NOS | 11 | (4.5) | 4 | (1.6) |
| Nausea | 10 | (4.1) | 6 | (2.5) |
| INFECTIONS AND INFESTATIONS | | | | |
| Upper respiratory tract infection NOS | 15 | (6.2) | 0 | (0.0) |
| NERVOUS SYSTEM DISORDERS | | | | |
| Headache NOS | 10 | (4.1) | 6 | (2.5) |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | | | | |
| Rash NOS | 8 | (3.3) | 0 | (0.0) |

Adapted from sponsor's electronic submission Trial C03 p 38

Note: Adverse events tabulated were those that were experienced by $\geq 3\%$ of all patients. The denominator for calculating percentages was the 243 patients who received at least one dose of Zegerid 40 mg.

Study OSB-IR C03 evaluated the efficacy and safety of Zegerid critically ill patients. Most of the patients in both the Zegerid and cimetidine groups had at least one AE, however, the sponsor reports of only 5 patients with drug-related AE in the Zegerid group: thrombocytopenia (1 patient), rash (2) and pyrexia (1) and hypotension (1). See table 7 below. All these are listed in the Prilosec label except for hypotension. A total of 115 patients (32.0%) experienced at least one SAE; Zegerid=61 patients, cimetidine=54 patients. These serious adverse events were all anticipated given the serious underlying disease in these patient population and reflected the severity of the underlying disease states for the patients.

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Table 7: Number (%) of Critically Ill Patients with Frequently Occurring Adverse Events (in ≥ 3% of Patients) by Body System and Preferred Term (OSB-IR-C03)

| MedDRA Body System Preferred Term | OSB-IR (N=178) | | Cimetidine (N=181) | |
|---|-------------------|------------------------------|-----------------------|------------------------------|
| | All AEs n (%) | Drug Related AEs n (%) | All AEs n (%) | Drug Related AEs n (%) |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | | | | |
| Anaemia NOS | 14 (7.9) | 0 (0.0) | 14 (7.7) | 0 (0.0) |
| Anaemia NOS Aggravated | 4 (2.2) | 0 (0.0) | 7 (3.9) | 0 (0.0) |
| Thrombocytopenia | 18 (10.1) | 1 (0.6) | 11 (6.1) | 4 (2.2) |
| CARDIAC DISORDERS | | | | |
| Atrial Fibrillation | 11 (6.2) | 0 (0.0) | 7 (3.9) | 0 (0.0) |
| Bradycardia NOS | 7 (3.9) | 0 (0.0) | 5 (2.8) | 0 (0.0) |
| Supraventricular Tachycardia | 6 (3.4) | 0 (0.0) | 2 (1.1) | 0 (0.0) |
| Tachycardia NOS | 6 (3.4) | 0 (0.0) | 6 (3.3) | 0 (0.0) |
| Ventricular Tachycardia | 8 (4.5) | 0 (0.0) | 6 (3.3) | 0 (0.0) |
| GASTROINTESTINAL DISORDERS * | | | | |
| Constipation | 8 (4.5) | 0 (0.0) | 8 (4.4) | 0 (0.0) |
| Diarrhoea NOS | 7 (3.9) | 0 (0.0) | 15 (8.3) | 1 (0.6) |
| Gastric Hypomotility | 3 (1.7) | 0 (0.0) | 6 (3.3) | 0 (0.0) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | | | |
| Hyperpyrexia | 8 (4.5) | 0 (0.0) | 3 (1.7) | 0 (0.0) |
| Oedema NOS | 5 (2.8) | 0 (0.0) | 11 (6.1) | 0 (0.0) |
| Pyrexia | 36 (20.2) | 1 (0.6) | 29 (16.0) | 0 (0.0) |
| INFECTIONS AND INFESTATIONS | | | | |
| Candidal Infection NOS | 3 (1.7) | 0 (0.0) | 7 (3.9) | 0 (0.0) |
| Oral Candidiasis | 7 (3.9) | 0 (0.0) | 1 (0.6) | 0 (0.0) |
| Sepsis NOS | 9 (5.1) | 0 (0.0) | 9 (5.0) | 0 (0.0) |
| Urinary Tract Infection NOS | 4 (2.2) | 0 (0.0) | 6 (3.3) | 0 (0.0) |
| INVESTIGATIONS | | | | |
| Liver Function Tests NOS Abnormal | 3 (1.7) | 0 (0.0) | 6 (3.3) | 1 (0.6) |
| METABOLISM AND NUTRITION DISORDERS | | | | |
| Fluid Overload | 9 (5.1) | 0 (0.0) | 14 (7.7) | 0 (0.0) |
| Hyperglycaemia NOS | 19 (10.7) | 0 (0.0) | 21 (11.6) | 0 (0.0) |
| Hyperkalaemia | 4 (2.2) | 0 (0.0) | 6 (3.3) | 0 (0.0) |
| Hypnatraemia | 3 (1.7) | 0 (0.0) | 9 (5.0) | 0 (0.0) |
| Hypocalcaemia | 11 (6.2) | 0 (0.0) | 10 (5.5) | 0 (0.0) |
| Hypoglycaemia NOS | 6 (3.4) | 0 (0.0) | 8 (4.4) | 0 (0.0) |
| Hypokalaemia | 22 (12.4) | 0 (0.0) | 24 (13.3) | 0 (0.0) |
| Hypomagnesaemia | 18 (10.1) | 0 (0.0) | 18 (9.9) | 0 (0.0) |
| Hyponatraemia | 7 (3.9) | 0 (0.0) | 5 (2.8) | 0 (0.0) |
| Hypophosphataemia | 11 (6.2) | 0 (0.0) | 7 (3.9) | 0 (0.0) |
| PSYCHIATRIC DISORDERS | | | | |
| Agitation | 6 (3.4) | 0 (0.0) | 16 (8.8) | 0 (0.0) |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS † | | | | |
| Acute Respiratory Distress Syndrome | 6 (3.4) | 0 (0.0) | 7 (3.9) | 0 (0.0) |
| Pneumothorax NOS | 1 (0.6) | 0 (0.0) | 8 (4.4) | 0 (0.0) |
| Respiratory Failure | 3 (1.7) | 0 (0.0) | 6 (3.3) | 0 (0.0) |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | | | | |
| Decubitus Ulcer | 6 (3.4) | 0 (0.0) | 5 (2.8) | 0 (0.0) |
| Rash NOS | 10 (5.6) | 2 (1.1) | 11 (6.1) | 2 (1.1) |
| VASCULAR DISORDERS | | | | |
| Hypertension NOS | 14 (7.9) | 0 (0.0) | 6 (3.3) | 0 (0.0) |
| Hypotension NOS | 17 (9.6) | 1 (0.6) | 12 (6.6) | 0 (0.0) |

Adapted from sponsor's electronic submission OSB-IR C03 p 78

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Note: Adverse events tabulated were those that occurred in $\geq 3\%$ of all patients in each treatment group. The denominator for calculating percentages was the number of ITT patients in each treatment group.

The frequently reported SAEs reflect the seriousness of the underlying medical conditions of the patient population. The higher level of sepsis at baseline in the Zegerid group 34.8%, compared with 28.7% in the cimetidine group possibly explain the incidence of thrombocytopenia (10.1%, compared with 6.1% in the cimetidine group) and pyrexia (20.2%, compared with 16.0% in the cimetidine group) in the Zegerid-treated patients. Seven patients in the Zegerid group had baseline thrombocytopenia compared to five patients in the cimetidine group. There were no clinically meaningful differences between the two treatment groups in terms of the numbers of patients with AEs by body system. Nosocomial pneumonia and clinically significant UGI bleeding were not included in the above table.

For UGI bleeding, there were 17 patients (Zegerid=7, cimetidine=10) that met the OSB-IR C03 protocol defined endpoint for UGI bleeding. There were 75 patients (Zegerid=27, cimetidine=48) who had macroscopic gastrointestinal bleeding which did not meet the endpoint for UGI bleeding. Three of these patients were withdrawn from the trial because of active UGI bleeding and one patient who was transferred to another hospital while actively bleeding. Three of these patients were in the cimetidine group and one was in the Zegerid group.

Nosocomial Pneumonia

Nosocomial pneumonia is a concern in critically ill patients. Drugs used to increase intragastric pH (e.g. antacids, H₂RAs and PPIs) may increase gastric colonization and therefore increasing the incidence of nosocomial pneumonia. The association between stress ulcer prophylaxis and nosocomial pneumonia had been widely debated; however, results of studies that have been conducted to assess this relationship has been inconsistent. After the start of the trial drug in study Zegerid C03, 14 (7.9%) patients in the Zegerid group developed nosocomial pneumonia compared to 11 (6.1%) in the cimetidine group ($p=0.54$). The sponsor analyzed this as a separate serious adverse event and the trial showed no evidence that administration of a daily dose of 40 mg increases the risk of developing nosocomial of pneumonia in critically ill patients compared with a continuous IV infusion of cimetidine.

Deaths

There were no deaths that occurred in the PK/PD trials (OSB-IR C02 and OSB-IR C05).

In the OSB-IR C07 trial, one patient died attributed to coronary artery disease 8 days after taking the trial medication. He is a 70 year old Caucasian male with a diagnosis of GU and esophageal ulcer, had a past medical history of hypertension,

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diabetes mellitus, diabetic neuropathy, coronary artery disease, a bypass graft 10 years ago, peripheral vascular disease, carotid artery disease, hyperlipidemia, obesity, hypothyroidism, gastrointestinal hemorrhage, anemia, left heel ulcer, and left leg cellulitis. This was considered by the investigator to be related to the patient's underlying medical condition and not to Zegerid 40 mg.

In the OSB-IR C03 trial, during the treatment period, there were a total of 48 deaths; Zegerid=27, cimetidine=21. During the post-trial follow-up period (2 to 30 days after the last day of trial drug administration), there were 43 deaths (Zegerid=25, cimetidine=18). None of the deaths were considered by the investigators to be related to the trial drug. Deaths in the Zegerid group during the trial and 30 days post-trial dose were numerically increased but not statistically significant. It is to be noted that the percentage of patients with ≥ 3 risk factors for UGI bleeding at baseline was slightly higher for the Zegerid group compared with the cimetidine group (69.1% vs. 64.6%). Patients in the Zegerid group have a more serious baseline disease characteristics when compared to the cimetidine group. The percentages of patients with acute renal failure, coagulopathy, and sepsis were at least 5%-6% higher at baseline in the Zegerid group compared to the cimetidine group. Moreover, the mean APACHE II score (a prognostic factor for mortality) for patients in the Zegerid group at baseline was significantly higher than that for patients in the cimetidine group (24.7 versus 22.7, respectively; $p=0.010$). Patients who died in the Zegerid group had a mean APACHE II score of 28 at baseline compared to 24.2 in the cimetidine group, which puts the Zegerid group at higher risk for mortality (~55% vs. ~40%).⁶

Safety Update:

The sponsor submitted a 120-day safety update on June 25, 2004. A 68 year old patient admitted to the trial after undergoing a craniotomy for a cerebellar pontine angle schwannoma received cimetidine as a trial drug treatment and developed UGI bleeding three days after endotracheal extubation and completion of trial participation. The bleeding led to transfusion of eight units packed red cells. The patient underwent an upper endoscopy which revealed an esophageal ulcer, superficial ulcerations of the esophagogastric junction, linear gastric erosions with visible vessels that were cauterized, and non-bleeding, chronic looking duodenal ulcerations. This event was considered by the investigator to be unrelated to the trial drug.

D. Adequacy of Safety Testing

This is a 505(b)(2) submission. For the trials in this NDA, the sponsor performed the appropriate safety monitoring for the subjects.

⁶ Emergency Medicine at NCEMI On line (www.ncemi.org): APACHE II Score Interpretation

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E. Summary of Critical Safety Findings and Limitations of Data

Zegerid 40 mg was well tolerated in patients with acid-related conditions when taken for 8-weeks and its safety profile was similar to that described in the Prilosec® labeling. In the critically ill patient population, adverse events related to the trial drug were nausea, vomiting, rash, pyrexia, hypotension and thrombocytopenia; all these are listed in the Prilosec label except for hypotension. Serious adverse events, including deaths were all anticipated given the serious underlying disease in these patient population and reflected the severity of the underlying disease states for the patients.

Overall, Zegerid 40mg appears safe to use for the proposed indications. The combination of postmarketing data, previous clinical trials and adverse events analysis with the studies (OSB-IR C02, C07 & C03) establish the safety of Zegerid. No new omeprazole related safety issues were identified in association with Zegerid treatment of critically ill patients and in patients with acid-related conditions.

Due to the sodium bicarbonate (1680mg) content of this formulation, it should be used with caution in patients who are sodium restricted, those who have problems with systemic acid-base balance, Bartter's syndrome, hypokalemia, and respiratory alkalosis. Known adverse reactions (rate unknown) with sodium bicarbonate include: abdominal pain, flatulence, hypernatremia, metabolic alkalosis, peripheral edema, seizures, tetany, and tremor. Long-term administration of bicarbonate with calcium or milk can cause milk-alkali syndrome. Sodium bicarbonate is contraindicated in patients with metabolic alkalosis and hypocalcemia.

VIII. Dosing, Regimen, and Administration Issues

Dose:

Omeprazole Sodium Bicarbonate - Immediate Release, Powder for Suspension (Zegerid) 40 mg

Proposed Indications:

- Treatment of Upper Gastrointestinal Bleeding in Critically Ill Patients
40mg initially followed by 40mg after 6 to 8 hours as a loading dose on the first day, then 40mg once daily
- Short-term Treatment of Benign Gastric Ulcer
40 mg once a day for 4 - 8 weeks

Zegerid 40mg should be taken at least one hour before eating.

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Directions for use: Empty packet contents into a small cup containing — water. Do not use other liquids or foods. Stir well, and drink immediately. Refill cup with water and drink.

If the suspension is to be administered through a nasogastric or orogastric tube, it should be constituted with approximately 20 mL of water and an appropriately-sized syringe should be used to administer the suspension into the tube, followed by a 20 mL water wash of the tubing.

No dosage adjustment is needed in the elderly. Dose adjustment in Asian subjects should be considered for maintenance of healing of erosive esophagitis. PK studies of single 20 mg omeprazole doses showed an approximately four-fold increase in AUC when compared to Caucasians. See Prilosec package insert.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

No new data regarding gender effects were submitted with this submission. There are no known differences in efficacy or safety based on gender with the use of omeprazole. In the OSB-IR C03 trial, 41% Zegerid treated patients were females and 59% were males. In the OSB-IR C02 crossover trial, 44% were female and 56% were males.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

There are no new data concerning the effect of *age* or *race* on safety and efficacy with the use of omeprazole were submitted this application. A total of 64 (36%) Zegerid treated patients in the OSB-IR-C03 trial were elderly (≥ 65 years of age); data indicate that Zegerid 40 mg is well tolerated in elderly patients.

In the Prilosec® package insert, it is reported that in Asians, PK studies of single 20 mg omeprazole doses showed an approximately four-fold increase in AUC when compared to Caucasians. Dose adjustment in Asian subjects should be considered for maintenance of healing of erosive esophagitis. There was one (0.6%) Asian patient in the OSB-IR C03 trial.

C. Evaluation of Pediatric Program

I recommend that the sponsor's request to waiver Pediatric Studies be denied and request for studies in the pediatric population.

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Similar to adults, children under physiologic stress can develop an imbalance in defensive factors responsible for maintaining a healthy gastrointestinal tract. Disruption of these defensive factors permits damage by aggressive factors to the upper gastrointestinal epithelium that may progress to stress ulceration and acute upper gastrointestinal tract bleeding (UGIB). Similar to the 20-24% in adults, studies that diagnosed UGIB based on macroscopic evidence of blood in gastric aspirates reported a 5-38% frequency in pediatric patients.⁷ We have a reason to believe that the pathophysiology of UGI bleeding in adults is similar in children, however, information on agents given for UGIB prophylaxis in pediatric patients is limited and data are extrapolated from adult studies to guide therapy.

New information in the area of UGIB prophylaxis and pediatric critical care is needed. Pediatric patients who are at high for bleeding, patients who are intubated, have shock, sepsis or extensive burns will benefit from this drug but the dose should be adjusted. Therefore, I recommend that the sponsor conduct a clinical outcome study that will supply information on the benefit of this drug in critically ill pediatric patients. The study can be an open-label, historical control trial. A PK/PD study to determine the appropriate dose in this population is recommended prior to initiating the clinical outcome study. These studies can be deferred at this time.

D. Comments on Data Available or Needed in Other Populations

Omeprazole has been used widely in the pediatric and geriatric population. No dosage adjustment is necessary when used in the elderly. Prilosec® is labeled for use in children as young as two years old. There is no available labeled liquid omeprazole formulation for patients in the pediatric age group.

Due to the sodium bicarbonate content of Zegerid, additional data in the renally impaired and in patients with acid-base imbalance will be informative.

X. Conclusions and Recommendations

A. Conclusions

The studies submitted in this NDA supports the use of Zegerid 40mg in the treatment of benign gastric ulcer and reduction of risk of UGI bleeding in critically ill patients.

Study OSB-IR C03 has demonstrated that Zegerid™ 40 mg is non-inferior and as efficacious as IV cimetidine in the reduction of risk of UGI bleeding in critically ill patients due to stress-related mucosal disease (SRMD). In addition, the equivalence in

⁷ Critl CM, UGI Bleeding in Critically Ill Patients, Pharmacotherapy 19(2):162-180, 1999

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AUC (0-inf) and PD effects shown by study OSB-IRC02 provides a bridge from Zegerid 40mg to the Agency's previous findings of safety and efficacy for Prilosec in the treatment of active benign gastric ulcer and also supportive for the indication of reduction of risk of UGI bleeding in critically ill patients. The ability of PPIs to raise intragastric pH and maintain an elevated pH in healthy volunteers as shown in study OSB-C02 suggests that PPIs supports their benefit in preventing SRMD.

Cimetidine, the only FDA approved drug for the prevention (reduction of risk) of UGI bleeding, requires dose adjustment in renally impaired patients. Continuous infusion of IV H₂RAs for >48 hours has been associated with tolerance in intragastric pH variability, likely due to enhanced gastrin-induced histamine production and competition of H₂RAs at the histamine subtype 2 receptor.⁸ Tolerance is not known to occur with PPIs. Reversible confusional states have been observed on occasion, predominantly, but not exclusively, in severely ill patients on cimetidine, this is reflected in the label. ICU patients are usually severely ill patients and therefore at risk for confusional states; omeprazole will be a good alternative for these patients.

Omeprazole has been proven safe and effective in the treatment of acid-related conditions for almost 15 years even at high doses (up to 120 mg three times a day); sodium bicarbonate, an excipient in this product, has been in use prior to 1938. It will be beneficial to have an FDA approved alternative drug available for the reduction of risk of UGI bleeding that has a wide margin of safety, few adverse effects and limited drug interactions.

Zegerid 40mg given once daily after a loading dose of 6 to 8 hours apart on the first day offers convenience in the schedule of drug administration. An IV line will not be necessary to administer this drug and therefore may lessen the tendency for phlebitis. Interruption of treatment due to unavailable IV line is also a possibility with cimetidine administration but not with oral Zegerid, however; an intact stomach and NGT/OGT in place are required for the administration of oral Zegerid.

No new safety concerns were identified in this NDA. The safety results from a safety study (OSB-IR C07) in patients with acid-related conditions taking Zegerid 40 mg for 8 weeks were similar with Prilosec® safety profile incorporated in the label. The safety results from the critically ill population (OSB-IRC03) were all related to the underlying disease of patients and severity of their illness.

A single study with 359 patients in 46 sites appears to be sufficient when compared to the cimetidine study where a total of 218 patients participated (in two pivotal studies).

⁸ R. Jung and R. Maclaren. *Annals of Pharmacotherapy*, Dec2002, pp 1929-1937.

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OSB-IR C03 trial enrolled patients who are at higher risk for UGI bleeding (all mechanically intubated with one other risk factor); critically ill patients are a difficult population to enroll. The results of the OSB-IR C03 has replicated the findings of the cimetidine trial (NDA 17-939, S-077) in the reduction of risk of UGI bleeding in critically patients. The link between reduction in gastric acidity and effectiveness in reduction of risk of UGI bleeding in critically ill patients is also supported by the FDA approval of IV cimetidine (an acid reducer) for this indication as well as by the routine "off-label" use by physicians of other H₂RAs and PPIs (IV pantoprazole and simplified omeprazole suspension by NG/OG tube). H₂RAs and PPIs are known to be effective in suppressing gastric acid and in treating various acid-related conditions. Therefore, there is substantial evidence that if cimetidine is efficacious in preventing UGI bleeding in critically ill patients then a PPI will also provide a similar therapeutic effect.

B. Recommendations

Omeprazole Sodium Bicarbonate-Immediate Release Powder for Oral Suspension (Zegerid™) 40 mg is recommended to be approvable by this medical officer for the following indications:

- Short-term Treatment of Benign Gastric Ulcer
- Reduction of risk of Upper Gastrointestinal Bleeding in Critically Ill Patients

Zegerid 40 mg should be taken at least one hour before meals after emptying the contents of packet into a small cup containing 2-3 oz of water. It is for adult use only; there are no adequate and well-controlled studies in pediatric patients for omeprazole containing sodium bicarbonate.

If the suspension is to be administered through a nasogastric or orogastric tube, it should be constituted with approximately 20 mL of water and an appropriately-sized syringe should be used to administer the suspension into the tube, followed by a 20 mL water wash of the tubing.

To get approval, the sponsor should incorporate the labeling recommendations listed in the Medical Officer's Labeling Review (see Appendix C) and the NDA team's labeling recommendations.

In addition, I recommend that the sponsor conduct a clinical outcome study that will supply information on the benefit of this drug in critically ill pediatric patients. The study can be an open-label, historical control trial. A PK/PD study to determine the appropriate dose in this population is recommended prior to initiating the clinical outcome study.

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XI. Appendix

APPENDIX A

Acute Physiology and Chronic Health Evaluation (APACHE II) Score Form

| PHYSIOLOGIC VARIABLE | HIGH ABNORMAL RANGE | | | | | LOW ABNORMAL RANGE | | | |
|--|--|----------|---------|-----------|---------------------|-----------------------|-----------|-----------------------|---------------------|
| | +4 | +3 | +2 | +1 | 0 | +1 | +2 | +3 | +4 |
| 1 TEMPERATURE - rectal (°C) | ≥41 | 39-40.9 | | 38.5-38.9 | 36.0-38.4 | 34-35.9 | 32-33.9 | 30-31.9 | ≤29.9 |
| 2 MEAN ARTERIAL PRESSURE - mm Hg (= 2 x diastolic + systolic) ÷ 3 | ≥160 | 130-159 | 110-129 | | 70-109 | | 50-69 | | ≤49 |
| 3 HEART RATE (ventricular response) | ≥180 | 140-179 | 110-139 | | 70-109 | | 55-69 | 40-54 | ≤39 |
| 4 RESPIRATORY RATE - (non-ventilated or ventilated) | ≥50 | 35-49 | | 25-34 | 12-24 | 10-11 | 6-9 | | ≤5 |
| 5 OXYGENATION: A-aDO ₂ or PaO ₂ (mm Hg) a) FIO ₂ ≥0.5: record A-aDO ₂ b) FIO ₂ <0.5: record only PaO ₂ | ≥500 | 350-499 | 200-349 | | <200 | | | | |
| | | | | | PO ₂ >70 | PO ₂ 61-70 | | PO ₂ 55-60 | PO ₂ <55 |
| 6 ARTERIAL pH (If no ABGs, record Serum HCO ₃ below*) | ≥7.7 | 7.6-7.69 | | 7.5-7.59 | 7.33-7.49 | | 7.25-7.32 | 7.15-7.24 | <7.15 |
| 7 SERUM SODIUM (mMol/L) | ≥180 | 160-179 | 155-159 | 150-154 | 130-149 | | 120-129 | 111-119 | ≤110 |
| 8 SERUM POTASSIUM (mMol/L) | ≥7 | 6-6.9 | | 5.5-5.9 | 3.5-5.4 | 3-3.4 | 2.5-2.9 | | <2.5 |
| 9 SERUM CREATININE (mg/dL) (Double Point for acute renal failure) | ≥3.5 | 2-3.4 | 1.5-1.9 | | 0.6-1.4 | | <0.6 | | |
| 10 HEMATOCRIT (%) | ≥60 | | 50-59.9 | 46-49.9 | 30-45.9 | | 20-29.9 | | <20 |
| 11 WHITE BLOOD COUNT (total/mm ³) | ≥40 | | 20-39.9 | 15-19.9 | 3-14.9 | | 1-2.9 | | <1 |
| 12 GLASGOW COMA SCALE (GCS). (Score = 15 minus actual GCS) | 15-GCS= | | | | | | | | |
| A Total Acute Physiology Score (APS) | Sum of the 12 individual variable points = | | | | | | | | |
| * Serum HCO ₃ (various mMol/L) Not preferred, use if no ABGs | ≥52 | 41-51.9 | | 32-40.9 | 22-31.9 | | 18-21.9 | 15-17.9 | <15 |

| Glasgow Coma Scale (Circle appropriate response) | | B Age | Points | C Chronic Health Points | APACHE II Score (sum of A+B+C) A APS points + B Age points + C Chronic Health Points = Total APACHE II |
|--|----------------------------------|--------------|--------|--|---|
| Eyes Opening | Verbal - <u>Non Intubated</u> | Age | Points | If the patient has a history of severe organ system insufficiency or is immuno-compromised assign points as follows: a. for nonoperative or emergency postoperative patients - 5 points or b. for elective postoperative patients - 2 points | |
| 4 - Spontaneously | 5 - Oriented and talks | ≤44 | 0 | | |
| 3 - Verbal command | 4 - Disoriented and talks | 45-54 | 2 | | |
| 2 - Painful stimuli | 3 - Inappropriate words | 55-64 | 3 | | |
| 1 - No response | 2 - Incomprehensible sounds | 65-74 | 5 | | |
| | 1 - No response | ≥75 | 6 | | |
| Motor | | Age points = | | LIVER: Cirrhosis with PHT or encephalopathy | |
| 6 - Verbal command | Verbal - <u>Intubated</u> | | | CARDIOVASCULAR: Class IV angina or at rest or with minimal self-care activities | |
| 5 - Localizes to pain | 5 - Seems able to talk | | | PULMONARY: Chronic hypoxemia or hypercapnia, polycythemia or PHT >40 mm Hg | |
| 4 - Withdraws to pain | 3 - Questionable ability to talk | | | KIDNEY: Chronic peritoneal dialysis or hemodialysis | |
| 3 - Decerebrate rigidity | 1 - Generally unresponsive | | | IMMUNE: Immuno-compromised host | |
| 2 - Decerebrate rigidity | | | | | |
| 1 - No response | | | | | |

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APPENDIX B Individual More Detailed Study Review

Clinical Trial OSB-IR-CO3

A Comparison of Omeprazole Immediate – Release Oral Suspension to Intravenous Cimetidine for the Prevention of Upper Gastrointestinal Bleeding in Critically Ill Patients

Study Period: June 4, 2002 to May 31, 2003

Ethics

This research was carried out in accordance with the clinical research guidelines established by the Basic Principles defined in the US 21 Code of Federal Regulations (CFR) Parts 50, 56, and 312 and the principles delineated in the latest version of the Declaration of Helsinki

Objectives

- To demonstrate that OSB-IR is efficacious in preventing upper gastrointestinal bleeding (UGI) bleeding in critically ill patients
- To demonstrate that OSB-IR is efficacious in maintaining an intragastric pH of > 4 in patients at risk for UGI bleeding due to stress-related mucosal damage (SRMD)
- To assess the safety and tolerability of OSB-IR patients at risk for UGI bleeding due to stress related mucosal disease (SRMD)

Study Design

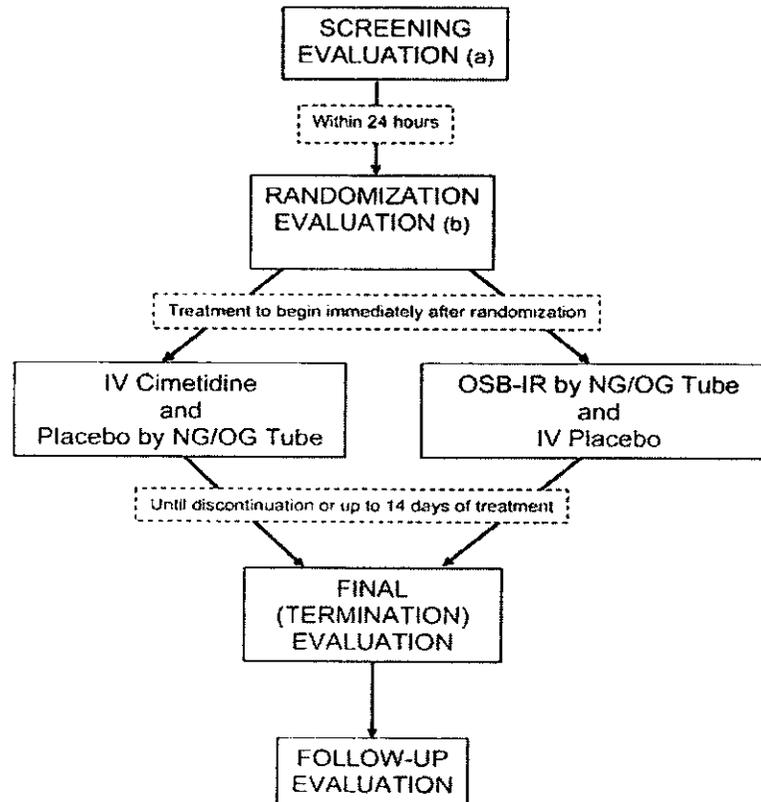
This was a triple-blind, double-dummy, prospective, multicenter, randomized clinical trial comparing the effectiveness and safety of OSB-IR oral suspension 40 mg to continuous IV cimetidine in the reduction of risk of UGI bleeding in critically ill patients at risk for SRMD. A total of 45 investigators at 46 clinical sites in the United States (US) participated in this trial.

Participants in this trial were critically ill patients who had been admitted to a critical/intensive care unit, who had a NG or OG tube in place, and expected to require at least 48 hours of mechanical ventilator support. Patients were to be randomized to one of two active drug regimens within 24 hours of screening. See Figure 1 and Table 1.

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Figure 1A: Trial Design Flow Chart



Adapted from sponsor's submission p.22

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Table 1A: Time and Events Table

| Procedure | Screening(a) | Randomization(b) | On Treatment(c) Days 1 → 14 | Final (Termination) Evaluation | Follow-Up Evaluation(d) |
|--|--------------|------------------|--|--------------------------------|-------------------------|
| Informed Consent | X | | | | |
| Medical History(e) | X | | | X | |
| Physical Examination | X | | | X | |
| APACHE II Assessment | X | | | X | |
| ISS Assessment (For Trauma Patients Only) | X | | | X | |
| Gastric Aspirates for Blood Assessment | X(f) | X(g) | Every 2 hrs for first 2 days, then every 6 hrs thereafter(h) | X | |
| Gastric Aspirates for pH Assessment | X | X | Every 2 hours for first 2 days, then twice/day thereafter(i) | X | |
| Chest Radiograph(j) | | X | If indicated | X | |
| Laboratory Tests(k) | X | If indicated | If indicated | If indicated | If indicated |
| Adverse Events | | | X | X | X |
| Concomitant Medications | | X | X | X | X |
| Concomitant Therapy (Blood Products) | | | If indicated | If indicated | If indicated |

Adapted from sponsor's electronic submission p 31

Note: APACHE II Assessment consisted of the following: temperature (rectal), mean arterial pressure, heart rate, respiratory rate, oxygenation, arterial pH (or serum HCO₃), Serum sodium, serum potassium, hematocrit, white blood cell count, Glasgow Coma Scale. See Appendix A for APACHE II Score Form.

- a The Screening and Randomization Evaluations may have occurred on the same day.
- b Randomization must occur within 24 hours of screening for the trial.
- c Treatment was to begin as soon as possible after randomization.
- d Follow-up Evaluation was to occur 24 hours after Termination Evaluation.
- e The medical history focused on current active medical problems and listed the number of risk factors present for UGI bleeding due to stress-related mucosal damage.
- f Two consecutive aspirates were to be taken at 1-hour intervals immediately before randomization, and were to be free of bright red blood and/or material with a coffee ground appearance.
- g The gastric aspirate taken immediately before randomization was to be free of bright red blood and/or material with a coffee ground appearance. (This aspirate sample may have been the 2nd of the two aspirates obtained during Screening Evaluation)
- h Gastric aspirates were to be assessed for blood by visual inspection. If coffee ground material was present, the presence of blood was confirmed with Gastrocult. i Chest radiographs were to be taken at Randomization and the Final (Termination) Evaluations. Interim chest

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radiographs were to be obtained as clinically indicated during treatment, if the patient had been diagnosed with or suspected of having nosocomial pneumonia.

- j Routine laboratory test results were to be collected at baseline for reference purposes. However, laboratory assessments were to be performed as needed for patient care and management. If blood was detected in a gastric aspirate, a hematocrit was to be obtained as a baseline and another was to be obtained 24 hours later using the local laboratory.
- k If blood was detected in a gastric aspirate, all blood products given to the patient in the following 24 hours were recorded.

Medical Officer Comments: The objectives are appropriate for the study and the study design appears adequate.

Study Population

Inclusion Criteria

- Adult or adolescent (≥ 16 years of age) males or non-pregnant females requiring mechanical ventilation for ≥ 48 hours
- An anticipated critical/intensive care unit stay of ≥ 72 hours
- An APACHE II score of > 11 immediately before randomization
- At least one other risk factor for UGI bleeding due to SRMD, in addition to mechanical ventilation. Acceptable risk factors included the following:
 - closed head injury
 - multiple trauma to head, chest, abdomen, solid organs, or limbs
 - major surgical procedures (e.g., mastectomy, pancreatectomy, cardiovascular surgery) 24 hours prior to screening
 - extensive burns ($\geq 30\%$ of the body surface area)
 - acute renal failure (urine output < 0.5 mL/kg of body weight/hour for 1 hour, despite adequate fluid resuscitation)
 - acid-base disorder ($\text{pH} \leq 7.3$ or base deficit ≥ 5.0 mmol/L with a plasma lactate level > 1.5 times the upper limit of normal for the reporting laboratory)
 - coagulopathy (a platelet count $< 50,000/\text{cmm}$, an International Normalized Ratio [INR] of > 1.5 [ic, prothrombin time > 1.5 times the control value], or a partial-thromboplastin time > 2 times the control value)
 - marked jaundice (defined as plasma total bilirubin concentration of > 51.3 $\mu\text{mol/L}$ or > 3 mg/dL)
 - coma
 - (either a systolic blood pressure < 80 mmHg for ≥ 2 hours or a decrease of ≥ 30 mmHg in the systolic blood pressure)
 - shock (arterial blood pressure ≤ 90 mmHg or mean arterial pressure ≤ 70 mmHg for at least 1 hour despite adequate fluid resuscitation, adequate intravascular volume status, or the use of vasopressors in an attempt to maintain a systolic blood pressure of ≥ 90 mmHg or a mean arterial pressure of ≥ 70 mmHg)
 - sepsis (defined as a positively cultured or clinically diagnosed infection with at least three of the following: a body temperature of $\geq 38^\circ\text{C}$ [$\geq 100.4^\circ\text{F}$] or \leq

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36°C [\leq 96.8°F], a heart rate of \geq 90 beats/min, tachypnea manifested by a respiratory rate of \geq 20 breaths/min, or hyperventilation as indicated by a carbon dioxide partial pressure (PaCO₂) of \leq 32 mmHg, and a white blood cell count of \geq 12,000 cells/cmm or \leq 4,000 cells/cmm, or the presence of $>$ 10% bands)

- An intact stomach, and an NG or an OG tube in place
- Anticipation of no enteral feedings for the first 2 days of trial drug treatment

Exclusion Criteria

- A status of "No Cardiopulmonary Resuscitation"
- Greater than 48 hours elapsed since the patient became eligible for the trial
- Known history of vagotomy, pyloroplasty, gastroplasty, or any other gastric surgery
- Known allergy to cimetidine or omeprazole
- Active gastrointestinal (GI) bleeding (including esophageal and gastric variceal bleeding, duodenal and gastric ulcers)
- Significant risk of swallowing blood (ie, severe facial trauma, oral lacerations, hemoptysis)
- Enteral feedings for the first 2 days of trial drug treatment (to avoid interference with determining secondary, pH analysis)
- Use of an investigational drug within 30 days prior to randomization
- Critical/intensive care unit admission following esophageal, gastric, or duodenal surgery or trauma
- Known history of UGI lesions that were likely to bleed (eg, esophageal or gastric varices, gastric polyps, tumors, etc. but excluding patients with gastric or duodenal ulcer disease)
- Any medical or surgical condition that precluded administration of an oral medication (ie, OSB-IR)
- End-stage liver disease

Medical Officer Comments: The inclusion and exclusion criteria are adequate for this study.

Removal of Patients from Therapy or Assessment

A patient could have been withdrawn from the trial at any time at either the investigator's discretion or the patient's or legally authorized representative's request. Patients who discontinued from the trial for AEs were to be treated and followed according to established medical practice. The reason for discontinuing from the trial was documented and could have included one of the following.

- Completion of 14 days of trial drug treatment with no clinically significant UGI bleeding
- Discharge from critical/intensive care unit before completing 14 days of trial drug treatment with no clinically significant UGI bleeding

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- Ventilatory extubation
- Development of clinically significant UGI bleeding (ie, patient met the bleeding endpoint as defined in the protocol)
- Death
- Development of any laboratory test abnormality(ies) such that the investigator deemed that the patient's continued participation in the trial to be ill-advised
- Use of unapproved concomitant medications
- Occurrence of intolerable AEs judged to be related to trial drug
- Withdrawal of consent by patient or patient's legally authorized representative
- Noncompliance with protocol
- Development of an intercurrent illness, injury, or medical condition likely to interfere with patient safety, trial assessments, or the required administration of trial drug
- Development of any condition for which the investigator felt treatment withdrawal was justified
- Termination or suspension of the trial by the sponsor or investigator for administrative reasons

Treatments

The following are the investigational products that will be used in this study:

- *OSB-IR powder for suspension (OSB-IR [PWD F/S])*
Formulation: 40 mg omeprazole/1680 mg sodium bicarbonate unit dose packets, each packet to be administered as a 20-mL aqueous suspension
- *Placebo powder for oral suspension*
6.2 g of excipients/unit dose packet. The contents of each packet are administered as a 20-mL aqueous suspension.
- *Cimetidine, intravenous (8 mL/vial)*
Aqueous, sterile solution containing 150 mg/mL cimetidine and 9 mg benzyl alcohol per mL
- *Placebo, intravenous*
Formulation: 0.9% Sodium Chloride Injection solution

A chest radiograph was obtained within 24 hours of randomization and a gastric aspirate was obtained immediately before randomization to exclude patients with active UGI bleeding (from any cause) and to assess the pH.

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Selection of Doses in the Trial

A 40-mg daily dose of OSB-IR with an additional first-day 40-mg loading dose 6 to 8 hours apart was chosen in this trial to achieve substantial gastric acid suppression as quickly as possible in patients at high risk for UGI bleeding.

The sponsor used a 300-mg loading dose of IV cimetidine, followed immediately by a continuous IV regimen of cimetidine at 50 mg/hour (25 mg/hour for patients whose creatinine clearance was < 30 cc/min), was the regimen specified in the pivotal trial supporting this labeling indication for cimetidine.

Medical Officer Comments: Cimetidine IV is the only FDA approved treatment for the prevention of upper GI bleeding in critically ill patients.

For the IV trial drug, doses were to be increased if a patient's intragastric pH was ≤ 4 on two consecutive occasions at least 1 hour apart on any day of treatment. Doses were to be increased as follows: the infusion rate was to be increased to 100 mg/hour and maintained at that rate until the patient discontinued or completed the trial. For patients who were receiving 25 mg/hour (5.2 mL/hour) due to impaired renal function, the infusion rate was to be increased to 50 mg/hour (10.4 mL/hour) and maintained at that rate until the patient discontinued or completed the trial.

Medical Officer Comments: The recommended dosing regimen for the prevention of gastrointestinal bleeding in adults using cimetidine is continuous I.V. infusion of 50 mg/hour. This recommendation can be found in the package insert of cimetidine. For patients requiring a more rapid elevation of gastric pH, continuous infusion may be preceded by a 150 mg loading dose administered by I.V. infusion. The infusion rate should be adjusted to individual patient requirements. This is reflected in the product's package insert. The sponsor used 300-mg loading dose of IV cimetidine in this trial because it was the regimen specified in the pivotal trial supporting the prevention of UGI bleeding labeling indication for cimetidine.

Administration of OSB-IR (40 mg/20 mL) or placebo suspension (20 mL) was to occur immediately after the patient was randomized and again 6 to 8 hours after the first dose. A suspension of 20 mL of trial drug (OSB-IR or matching placebo) was then to be given by NG/OG tube once daily at approximately the same time each morning, starting on the second day of trial treatment and continuing until the patient discontinued from the trial. For patients who received enteral feedings on Day 3 through Day 14, the feedings were stopped for approximately 3 hours predose and 1 hour postdose.

The dose was increased if a patient's intragastric pH was ≤ 4 on two consecutive occasions at least 1 hour apart on any day of treatment. The dose of the oral trial drug was to be increased by administering an additional 40 mg (i.e., 80 mg total for the day) of omeprazole or matching placebo when a second intragastric pH of ≤ 4 was recorded, at least 1 hour after the first, for that day. This increased dosage for the oral trial drug was not to be continued on

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subsequent treatment days (ie, dose returned to 40 mg daily) unless the intragastric pH was again ≤ 4 for two consecutive occasions at least 1 hour apart for each of the subsequent treatment days.

No adjustments were to be made in the dosage of the oral trial drug for elderly patients or patients with renal impairment.

The total daily dose of omeprazole was not to exceed 80 mg (40 mL) on any treatment day, except Day 1, on which the maximum daily dose was not to exceed 120 mg (60 mL).

Medical Officer Comments: It should be noted that the more oral omeprazole powder for suspension is given, the more amount of sodium bicarbonate is administered. Each 40mg of omeprazole suspension contains 20 mEq of sodium bicarbonate; therefore, it is possible that on the first day, a patient could receive a maximum of 60 mEq of sodium bicarbonate and/or 40mEq on subsequent days.

Blinding

The placebos were matched in appearance to their respective active trial drugs. All patients, site personnel (including investigators, pharmacists, staff nurses, and coordinators), laboratory personnel, personnel at Santarus, and the medical monitor were blinded to the trial treatment assigned to each patient.

Prior and Concomitant Therapy

The following therapies are prohibited after enrollment:

- Other investigational drug(s)
- Proton pump inhibitors, H₂RAs, or antacids not specified by the protocol

Medical Officer Comments: Patients should be excluded if they had received H₂RAs within 12 hours of admission to the study or treatment within 24 hours before admission to the study with omeprazole. These medications might affect results of gastric pH.

Enteral Feedings

Enteral feedings were to be permitted *on or after the third day* of trial drug administration if it was in the best interest of the patient. The following enteral feeding schedule was recommended for this trial:

- On Day 1 and Day 2, no enteral feedings were to be permitted.
- On Day 3 through Day 14, enteral feedings were to be permitted as follows:
 - Intermittent enteral (intragastric and postpyloric) feedings were to be permitted from approximately 0800 hours on one day to 0300 hours on the following day. Enteral feedings were to be suspended from 0300 to 0700 hours each day to

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- allow sufficient time for the contents of the feeding to pass through the pylorus and to permit the administration of oral trial drug into an empty stomach.
- Oral trial drug was to be administered by NG/OG tube approximately 3 hours after the suspension of enteral feeding. Enteral feeding was to be resumed approximately 1 hour after each oral trial drug administration.

Medical Officer Comments: Enteral nutrition can be an effective therapy to prevent stress ulcer formation. Intensive care unit patients receiving enteral nutrition have less gastrointestinal bleeding presumably due to gastric acid neutralization by the enteral feeding solution. However, enteral feedings not only increase gastric pH but also increase gastric distention, both of which are associated with gastric colonization.⁹

Efficacy and Safety Variables

Efficacy Measurements

Efficacy was to be evaluated by the occurrence of clinically significant UGI bleeding and by intragastric pH levels determined from gastric aspirates.

The schedule for gastric aspirate sampling is provided in the table below. Gastric aspirates were to be collected according to the following schedule:

Table 2A : Gastric Aspirate Sampling

| Parameter | Days 1 and 2 | Days 3 through 14 |
|--------------------------------|---------------|---|
| Assessment of UGI bleeding | Every 2 hours | Every 6 hours In patients receiving enteral feedings, an assessment was to be taken approximately 3 hours after suspension of enteral feeding (or just prior to oral trial drug administration). An additional assessment was to be taken 1 hour following oral trial drug administration. |
| Measurement of intragastric pH | Every 2 hours | Immediately before and 1 hour following oral trial drug administration |

Adapted from sponsor's electronic submission TrialOSB-IR CO3 p32

Medical Officer Comments: The gastric aspirate sample obtained one hour after oral trial drug administration might reflect the antacid effect of omeprazole powder for suspension (which contains sodium bicarbonate) on the gastric pH. Therefore, one has to pay more attention to the pre-dose gastric pH value of the following dose, which is more a reflection of the effect of omeprazole on the gastric pH.

⁹ Reilly J, Fennerty B; J of Pharm Prac, Dec. 1998, pp 418-436.

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On Day 1 and Day 2

If enteral feeding was initiated, it was to be temporarily suspended at least 3 hours prior to scheduled NG or OG dosing of trial drug. Any residual food was to be removed from the stomach 3 hours after stopping enteral feeding and a gastric aspirate was to be obtained approximately 3 hours after suspension of enteral feeding, followed immediately by trial drug administration. The next gastric aspirate was to be assessed approximately 1 hour following trial drug administration, before resumption of enteral feeding. Routine aspirate assessment was to continue every 6 hours.

If other medical interventions precluded gastric aspirate sampling at the designated sampling intervals, sampling should have occurred at the next scheduled time point following completion of each medical intervention.

Gastric pH was to be measured on aliquots of gastric aspirates taken immediately before and 1 hour after oral trial drug administration in all patients. The NG or OG tube was to be clamped for 1 hour following the administration of oral trial drug, if feeding was to occur, or 2 hours if suction was to be resumed.

At each sampling interval while patients were on gastric suction, all fluid was to be discarded from the collection units so that each gastric aspirate represented the fluid collected over the respective sampling interval.

Assessment of Blood in Nasogastric or Orogastric Aspirates

Gastric aspirates were collected every 2 hours on Day 1 and Day 2 and every 6 hours on Day 3 through Day 14 (whether or not the patient was being fed enterally) and were inspected for gross evidence of bleeding (i.e., presence of bright red blood that did not clear with lavage or coffee ground material). Gastric aspirates containing coffee ground material were tested using Gastrocult to confirm the presence of blood. In addition, at least two additional gastric aspirates were to be obtained within 2 to 4 hours (at least 60 ± 20 minutes apart) of the aspirate containing the coffee ground material.

Measurement of Intra-gastric pH

The pH of gastric aspirates was measured using a portable, digital pH meter.

Upper Endoscopy

The confirmation of UGI bleeding by upper endoscopy was not required in this trial. However, if the investigator (or attending physician and/or team) believed that it was clinically indicated, an upper endoscopy could have been performed to identify the source of bleeding.

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Safety

Adverse Events and Serious Adverse Events

Safety was to be assessed by evaluating the severity, duration, and relationship to trial treatment of AEs and SAEs. The use of concomitant medications, changes from baseline in physical examination findings, chest radiographs, clinical laboratory test results, and vital signs measurements were conducted according to the schedule presented. All safety information was to be documented within the patient's medical records and CRF unless otherwise noted. Occurrences of non-endpoint UGI bleeding, UGI bleeding that met the primary endpoint, and occurrences of nosocomial pneumonia were tabulated separately from all other AEs.

Laboratory Measurements

At Screening and at Termination, the following laboratory test results were to be measured and used to calculate the APACHE II Scores:

- serum sodium (mMol/L),
- arterial pH (or serum bicarbonate if no arterial blood gases were measured, mMol/L),
- serum potassium (mMol/L),
- serum creatinine (mg/dL),
- hematocrit (%), and
- white blood count (total/cmm)

Hematocrit was to be measured at the start of UGI bleeding (within 1 hour) and 24 hours later (within 2 hours) in all patients with clinically significant UGI bleeding.

Evaluation of Nosocomial Pneumonia

Nosocomial pneumonia was to be assessed by comparing a baseline chest radiograph (within 24 hours of randomization into the trial) and an exit chest radiograph (within 48 hours after the trial drug was stopped). The following criteria had to be met before a patient could be diagnosed with nosocomial pneumonia:

- Onset of symptoms that occurred within the following times:
 - ≥ 72 hours after admission to an acute care hospital
 - ≤ 7 days after a patient was discharged from the hospital. The patient's initial hospitalization must have been ≥ 3 days duration.
- Presence within 48 hours of screening of a new or evolving infiltrate on a CXR not related to another disease process or condition (eg, congestive heart failure or acute respiratory distress syndrome)

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- New onset of production of purulent sputum or an increase in volume of purulent sputum and the presence of at least one of the following:
 - Fever (oral: $T^{\circ} \geq 38^{\circ}\text{C}/100.4^{\circ}\text{F}$, tympanic: $T^{\circ} \geq 38.5^{\circ}\text{C}/101.2^{\circ}\text{F}$, or a rectal/core: $T^{\circ} \geq 39^{\circ}\text{C}/102.2^{\circ}\text{F}$) or hypothermia (rectal/core $T^{\circ} < 36^{\circ}\text{C}/96.8^{\circ}\text{F}$) or oral $T^{\circ} < 35.5^{\circ}\text{C}/95.9^{\circ}\text{F}$)
 - Leukocytosis (total peripheral white blood cell count $>10,000/\text{cmm}$)
 - $>15\%$ bands, regardless of total peripheral white blood cell count
 - Leukopenia (total white blood cell count $< 4,500/\text{cmm}$)

A diagnosis of nosocomial pneumonia was to be confirmed by either positive sputum culture or positive results from a Gram stain. A lower respiratory tract specimen of good quality was to be collected within 48 hours before treatment for the infection was initiated.

Medical Officer Comments: Safety assessments appear adequate for this trial.

Efficacy

Primary Efficacy Endpoint

The occurrence of clinically significant UGI bleeding in critically ill patients. Clinically significant UGI bleeding was defined as follows:

On Day 1 and Day 2:

- Bright red blood per NG or OG tube that did not clear after NG or OG tube adjustment and 5 to 10 minutes of lavage with room temperature normal saline, or
- Persistent Gastrocult-positive coffee ground material for at least eight consecutive hours that did not immediately clear after at least 100 mL of lavage with room temperature normal saline.

Medical Officer Comments: In the trials conducted for the approval of cimetidine IV for the prevention of stress related upper GI bleeding in critically ill patients, the endpoint, the second bullet reads:

- **Persistent Gastrocult-positive coffee ground material for at least eight consecutive hours that did not immediately clear after at least 100 mL lavage and/or which were accompanied by a drop in hematocrit of 5 percentage points. In this trial, a drop in hematocrit of 5 percentage points was not included in the primary endpoint.**

On Day 3 through Day 14:

- Bright red blood per NG or OG tube that did not clear after NG or OG tube adjustment and 5 to 10 minutes of lavage with room temperature normal saline, or
- Persistent Gastrocult-positive coffee ground material in at least three consecutive gastric aspirates within 2 to 4 hours (at least 60 ± 20 minutes apart) that did not

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immediately clear after at least 100 mL of lavage with room temperature normal saline.

If a patient was being fed enterally and either bright red blood or coffee ground material was observed in the gastric aspirate, enteral feeding was to be stopped. If bright red blood was observed and it did not clear after NG or OG tube adjustment and 5 to 10 minutes of lavage, the primary efficacy endpoint was met. If Gastrocult-positive coffee ground material was observed and it did not clear with 100 mL of lavage, additional gastric aspirates were to be taken 1 and 2 hours later. If Gastrocult-positive coffee ground material was observed at both 1 and 2 hours, the primary efficacy endpoint was met.

Secondary Efficacy Assessments

- The median gastric pH on Day 1 and on Day 2
- The median predose and median postdose gastric pH on Day 3 through Day 14
- The median postloading dose (oral trial drug) gastric pH
- The percent of patients with a median gastric pH > 4 on Day 1 and on Day 2
- The percent of patients receiving a trial drug dose increase for gastric pH \leq 4

Ethics

To ensure that all procedures were in compliance with Good Clinical Practices, FDA guidelines, and according to federal law.

Statistical Methods Planned in the Protocol and Determination of Sample Size

All analyses were performed, and all tables, data listings, and figures were prepared using SAS version 8.2. Summary statistics for continuous variables included the mean, standard deviation, median, minimum, and maximum value. Categorical variables were presented as counts and percentages. Means, standard deviations, median values, and percentages were rounded to one decimal place. Minimum and maximum values were presented in their recorded units. Variables measured at Screening were considered the Baseline values for all analyses.

Primary Efficacy Non-Inferiority Analysis

A non-inferiority analysis was used to evaluate whether or not OSB-IR is as effective as cimetidine in preventing UGI bleeding in critically ill patients. The null (H_0) and alternative (H_a) hypotheses that were tested in the non-inferiority analysis were:

$$H_0: p_{\text{OSB-IR}} \geq p_{\text{cimetidine}} + \delta \text{ versus } H_a: p_{\text{OSB-IR}} < p_{\text{cimetidine}} + \delta, \quad (1)$$

where p represents the proportion of patients who experienced UGI bleeding, and where H_0 expresses the null hypothesis condition that the bleeding rate for OSB-IR exceeds the bleeding rate for cimetidine by an amount at least as large as δ . H_a expresses the

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alternative condition that the bleeding rate for OSB-IR might exceed the rate for cimetidine, but by an amount that is not greater than δ .

H_0 was tested by constructing the following one-sided, 97.5% ($\alpha = 0.025$) confidence interval for the difference in bleeding rates between OSB-IR and cimetidine:
 $-1, p_{\text{OSB-IR}} - p_{\text{cimetidine}} + Z_{\alpha=0.025}(\text{SE})$, (2)

where:

$\text{SE} = [p_{\text{OSB-IR}}(1 - p_{\text{OSB-IR}})/n_{\text{OSB-IR}} + p_{\text{cimetidine}}(1 - p_{\text{cimetidine}})/n_{\text{cimetidine}}]^{1/2}$,

and where n is the number of patients in either the OSB-IR or cimetidine treatment groups. If the upper bound of this confidence interval did not enclose δ (0.05), it was to be concluded that OSB-IR is not inferior to cimetidine in the prevention of UGI bleeding.

Superiority Analysis

If it was concluded that OSB-IR is not inferior to cimetidine, then a superiority comparison was to have been conducted using the method of Dunnett and Gent (1977). Using this method, the following two one-sided hypotheses were to be tested:

$H_{01}: p_{\text{OSB-IR}} \geq p_{\text{cimetidine}} + \delta$ versus $H_{a1}: p_{\text{OSB-IR}} < p_{\text{cimetidine}} + \delta$,

and $H_{02}: p_{\text{OSB-IR}} - p_{\text{cimetidine}} > 0$ versus $H_{a2}: p_{\text{OSB-IR}} - p_{\text{cimetidine}} < 0$,

where, as before, p represents the proportion of patients with UGI bleeding. Note that H_{01} and H_{a1} are the same hypotheses tested in the non-inferiority analysis (1). Rejection of both H_{01} and H_{02} supports the superiority of OSB-IR when compared with cimetidine. If H_{01} was not rejected in the non-inferiority analysis, H_{02} would not have been tested, since both H_{01} and H_{02} must be rejected to conclude that OSB-IR is superior to cimetidine in preventing UGI bleeding. H_{01} and H_{02} were to be tested at significance levels $\alpha_1 = 0.025$ and $\alpha_2 = 0.05$, respectively. If there is non-inferiority but not superiority, then the overall probability of concluding superiority using this two step, sequential procedure is 0.05.

Additional Analyses of the Primary Efficacy Endpoint

For patients who met the primary efficacy endpoint, the association between the following

variable values at Baseline and treatment group were to be assessed:

- The number of risk factors present at Baseline, categorized as 2, ≥ 3
- Baseline pH, categorized as < 2.0 , 2.0 to 4.0, 4.1 to 5.9, ≥ 6.0
- The mean Baseline APACHE II score
- The trial day that bleeding occurred, categorized as Day 1, 2, 3 to 7, ≥ 8 was to be tabulated by treatment group.

For patients who met the primary efficacy endpoint and who had a hematocrit measured at the start (within 1 hour) of bleeding and 24 hours later (within 2 hours), the percent change in hematocrit between the two measurements was calculated as:

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100 x (24 hour - 1hour) / 1hour and is presented in a data listing. This listing indicates whether or not blood products were received for UGI bleeding in the time interval between the two hematocrit measurements.

Secondary Efficacy Analyses

Given the nature and severity of the conditions of patients in this trial, it was expected that other medical interventions may have precluded gastric aspirate sampling at the designated times on any trial day. In addition, patients could have left the trial at any time. Therefore, only the available data for each patient were used in the secondary efficacy analyses that are described in the following sections, and no attempt was made to impute missing data.

Median Gastric pH on Trial Day 1 and Day 2

The median gastric pH was to be calculated separately for each patient for Day 1 and Day 2, and was to be compared by treatment group using the Wilcoxon Rank Sum test.

Median Predose Gastric pH on Trial Day 3 through Day 14

The median predose gastric pH was calculated for each patient for the Day 3 through Day 7 interval and for the Day 8 through Day 14 interval, and was compared by treatment group using the Wilcoxon Rank Sum test. For this analysis, the predose gastric pH was the last gastric pH measurement taken prior to the administration by NG/OG tube of trial drug for the Day 3 through Day 14 interval.

Median Postdose Gastric pH on Trial Day 3 through Day 14

The median postdose gastric pH was calculated for each patient for the Day 3 through Day 7 interval and for the Day 8 through Day 14 interval, and was compared by treatment group using the Wilcoxon Rank Sum test. For this analysis, the postdose gastric pH was the gastric pH measurement taken one hour after the administration by NG/OG tube of trial drug for the Day 3 through Day 14 interval.

Median Postloading Dose Regimen (Oral Trial Drug) Gastric pH

The median gastric pH taken two hours after the second dose of oral trial drug, whether received on Day 1 or Day 2, was presented graphically by treatment group.

Percent of Patients with a Median Gastric pH > 4 on Day 1 and Day 2

The median gastric pH was calculated for each patient for Day 1 and Day 2. The percent of patients with a median gastric pH > 4 on Day 1 and Day 2 was compared by treatment group using the Fisher's Exact test.

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Failure / Loss of Adequate Gastric pH Control (pH \leq 4)

Control of gastric pH was considered inadequate if the gastric pH was \leq 4 for measurements of two consecutive gastric aspirates, at least one hour apart, on any trial day. This definition of adequate control triggered directions for increasing the dose of both the oral and IV trial drug. The proportion of patients with at least one episode (two aspirates) of inadequate control was compared by treatment group using the Fisher's Exact test. Adequate pH control was considered to have been lost if patients who had a median daily gastric pH on Day 3 of $>$ 4 had a median gastric pH $<$ 4 on the last day that pH measurements were available.

Safety Analyses

The analysis of safety included all ITT patients.

Nosocomial Pneumonia

Nosocomial pneumonia was considered a serious, severe, and expected AE. The number and percent of patients diagnosed with nosocomial pneumonia were compared by treatment group using the Fisher's Exact test.

Non-Primary Endpoint Gastric Bleeding

Incidences of gastric bleeding that occurred during the trial, but that did not meet the criteria of the primary efficacy endpoint for this trial, are presented separately in a data listing.

Interim Safety Analysis

The accumulation of unexpected trial drug events was not anticipated with omeprazole and cimetidine. If SAEs or deaths exceeded expected rates (ie, if deaths exceeded 30%, nosocomial pneumonia exceeded 40%) or if there was an accumulation of any particular unexpected AE, an independent reviewer or a Data Safety Monitoring Board (DSMB) was asked to examine the unblinded safety data and make recommendations. The need for an independent review of the safety data for this trial did not arise.

Patient Evaluability

The numbers of ITT and PP patients were tabulated by treatment group.

Laboratory Measurements

The APACHE II classification system categorizes ranges of selected laboratory test results by the degree of abnormality, and is a reliable and validated measurement of illness severity in critically ill patients. The number and percent of patients with

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abnormally low, normal, and abnormally high laboratory test results at Baseline and Termination were tabulated by treatment group.

Changes in the Conduct of the Trial or Planned Analyses

Amendments

One amendment to the protocol was made on April 10, 2002, prior to trial start, in order to accommodate input from the FDA. The following changes were made to the protocol in Amendment 1:

- Trial title was revised (ie, "...Prevention of Upper Gastrointestinal Bleeding Due to Stress-Related Mucosal Damage" was changed to "...Prevention of Upper Gastrointestinal Bleeding in Critically Ill Patients").
 - The wording of the first trial objective, trial design section, and all other relevant sections were revised to reflect the change in the title of the trial.
 - The medical monitor was changed.
 - The number of patients to be enrolled was changed from 108 to 142 PP patients in each of the two treatment groups.
 - Clarification was added that gastric lavages were to be performed using room temperature saline.
 - Definitions for intragastric pH endpoints were added (ie, proportion of patients with a median gastric pH > 4, time gastric pH was > 4, proportion of patients requiring an increase in dose of trial drug to maintain intragastric pH level of > 4).
 - Laboratory testing was added to the screening procedures.
 - The risk factor "major surgical procedures" was added to the inclusion criteria.
 - The bilirubin ranges were changed (ie, > 513 $\mu\text{mol/L}$ or > 30 mg/dL to > 51.3 $\mu\text{mol/L}$ or 3.0 mg/dL) for the marked jaundice risk factor inclusion criterion (correction of typographical error).
 - Timing of enteral feedings was adjusted and the collection times for gastric aspirate samples was changed to reconcile with this change in feeding times.
 - The data collection procedures for nosocomial pneumonia were clarified.
 - The level of significance was changed from 0.05 to 0.025 in the statistical analysis procedures for the primary endpoint.
 - The PP population was defined.
 - Intent-to-treat population was added to the primary analysis in addition to the PP population.
 - Analysis of secondary endpoints was clarified.
 - Procedures for administrative analysis were clarified.
 - Investigators' responsibilities in collecting SAE data was revised.
 - Clarification of procedures for any interim analysis was added.
- Amendment 1 changes were made before any patients were enrolled into this trial.

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Results

Patient Accounting

Table 3A: Summary of Patient Disposition

| Patients | OSB-IR | Cimetidine | Total |
|---------------------------------|------------|------------|------------|
| | (N=178) | (N=181) | (N=359) |
| | n (%) | n (%) | n (%) |
| Exposed to trial drug | 178 | 181 | 359 |
| Completed | 124 (69.7) | 140 (77.3) | 264 (73.5) |
| Discontinued due to: | | | |
| Death | 15 (8.4) | 15 (8.3) | 30 (8.4) |
| Abnormal laboratory test result | 5 (2.8) | 5 (2.8) | 10 (2.8) |
| Drug-related AE | 2 (1.1) | 2 (1.1) | 4 (1.1) |
| NG/OG tube removal | 14 (7.9) | 7 (3.9) | 21 (5.8) |
| Administrative | 18 (10.1) | 12 (6.6) | 30 (8.4) |

Adapted from sponsor's electronic submission CO3 p. 49

Note: A patient was considered to have completed the trial if the patient

- 1) completed 14 days of trial drug treatment with no clinically significant UGI bleeding
- 2) was discharged from the critical/intensive care unit before completing 14 days of trial drug treatment with no clinically significant UGI bleeding
- 3) had ventilatory extubation or
- 4) developed clinically significant UGI bleeding (the protocol-specified endpoint).

The denominator for calculating percentages was the number of ITT patients in each treatment group (or total number of ITT patients).

Medical Officer Comments: A total of 359 patients entered the trial and were exposed to the trial drug; 178 patients for OSB-IR and 181 for cimetidine. A total of 264 patients (73.5%) completed the trial; 124 (69%) for OSB-IR and 140 (77.3%) for cimetidine.

The disposition of patients was similar for the OSB-IR group and the cimetidine group.

The most common protocol deviations in this trial were

- 1) trial drug administration and dose adjustment errors,
- 2) failure to obtain gastric aspirate pH samples, and
- 3) enrolled patients that did not meet the inclusion/exclusion criteria specified in the protocol.

In spite of these deviations, drug compliance during the trial was good. Protocol exemptions were granted for two main reasons;

- 1) greater than stipulated time interval of ≤ 48 hours from arrival of patients at the emergency room until entrance in the trial, and
- 2) start of enteral feeding prior to the first dose administration of oral trial medication (enteral feedings were subsequently discontinued for these patients).

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Efficacy Evaluation

Table 4A: Summary of Analysis Populations

| Analysis Populations | OSB-IR N (%) | Cimetidine N (%) | Total N (%) |
|-----------------------|-----------------|---------------------|----------------|
| Intent-to-Treat (ITT) | 178 (100.0) | 181 (100.0) | 359 (100.0) |
| Per-Protocol (PP) | 157 (88.2) | 146 (80.7) | 303 (84.4) |

Adapted from sponsor's electronic submission CO3 p50

The ITT population consists of all randomized patients who received at least one dose of trial drug. A patient was included in the PP population if:

- 1) all major inclusion and exclusion criteria were satisfied
- 2) at least 50% of the scheduled gastric blood and pH assessments were completed
- 3) all scheduled doses of trial drug by NG/OG tube were received within 12 hours of the scheduled dosing up to the time of discontinuation/completion
- 4) all scheduled IV doses of trial drug were received for at least 12 of every 24 hours up to the time of discontinuation/ completion, and
- 5) the appropriate increases in the doses of trial drugs were received within 12 hours of developing the stipulated criteria.

The denominator for calculating percentages was the number of ITT patients in each treatment group (or total number of ITT patients).

The PP patient population was used for the assessment of the primary efficacy endpoint. The ITT population was used for all other analyses, including the assessment of the primary efficacy endpoint.

Of the 56 patients (21, OSB-IR group and 35, cimetidine group) excluded from the PP population, 29 (51.8%) were excluded because protocol-specified dose increases were not administered. This included 4 (19.0%) OSB-IR-treated patients and 25 (71.4%) cimetidine treated patients. The lower percentage of cimetidine-treated patients in the PP population is principally the result of a failure to increase the cimetidine dose within 12 hours of developing the stipulated criteria. The sponsor reports that given the severity of the medical conditions present in the patient population, requiring continuous monitoring and interventions, this type of protocol deviation was expected.

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Demographic and Other Baseline Characteristics

Table 5A: Baseline Demographics

| Baseline Demographics | OSB-IR (N=178) n (%) | Cimetidine (N=181) n (%) |
|-----------------------|----------------------------|--------------------------------|
| Age (years) | | |
| n | 178 | 181 |
| Mean | 54.9 | 56.5 |
| SD | 18.3 | 18.5 |
| Min | 16 | 16 |
| Max | 91 | 90 |
| Age (years) | | |
| < 65 | 114 (64.0) | 117 (64.6) |
| ≥ 65 | 64 (36.0) | 64 (35.4) |
| Sex | | |
| Female | 73 (41.0) | 76 (42.0) |
| Male | 105 (59.0) | 105 (58.0) |
| Race | | |
| Caucasian | 115 (64.6) | 115 (63.5) |
| Black | 52 (29.2) | 47 (26.0) |
| Asian | 1 (0.6) | 1 (0.6) |
| Hispanic | 7 (3.9) | 17 (9.4) |
| Other | 3 (1.7) | 1 (0.6) |

Adapted from sponsor's electronic submission CO3 p 52

Note: The denominator for calculating percentages was the number of ITT patients in each treatment group.

Medical Officer Comments: The mean age of the patients in the trial is 55 years with an age range between 16 to 90 years. There were more males (58.5%) than females (41.5%). The majority of patients were Caucasians (64%), followed by blacks (28%). The treatment groups were well balanced in terms of demographics except that there were more Hispanics, in the Cimetidine group, 9.4% compared to the OSB-IR group, 3.9%.

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Baseline disease characteristics for these critically ill patients, including risk factors for UGI bleeding are presented in the next table.

Table 6A: Summary of Disease Characteristics at Baseline

| Baseline Characteristics | OSB-IR (N=178) n (%) | Cimetidine (N=181) n (%) | P-Value* |
|---|----------------------------|--------------------------------|----------|
| Number of additional risk factors for UGI bleeding | | | 0.373 |
| 2 | 55 (30.9) | 64 (35.4) | |
| ≥ 3 | 123 (69.1) | 117 (64.6) | |
| Additional risk factors for UGI bleeding | | | |
| Hypotension | 47 (26.4) | 51 (28.2) | |
| Closed-head injury | 22 (12.4) | 25 (13.8) | |
| Multiple trauma | 29 (16.3) | 37 (20.4) | |
| Major surgical procedure | 38 (21.3) | 42 (23.2) | |
| Extensive burns | 3 (1.7) | 4 (2.2) | |
| Acute renal failure | 47 (26.4) | 33 (18.2) | |
| Acid-base disorder | 58 (32.6) | 56 (30.9) | |
| Coagulopathy | 37 (20.8) | 26 (14.4) | |
| Marked jaundice | 0 (0.0) | 1 (0.6) | |
| Coma | 33 (18.5) | 38 (21.0) | |
| Shock | 34 (19.1) | 34 (18.8) | |
| Sepsis | 62 (34.8) | 52 (28.7) | |
| APACHE II Score | | | 0.010 |
| N | 178 | 181 | |
| Mean | 24.7 | 22.7 | |
| SD | 7.5 | 7.1 | |
| ISS (for trauma patients only) | | | 0.786 |
| N | 39 | 47 | |
| Mean | 30.8 | 31.5 | |
| SD | 11.5 | 13.8 | |
| Gastric pH | | | 0.514 |
| Missing | 1 (0.6) | 1 (0.6) | |
| < 2.0 | 18 (10.1) | 12 (6.6) | |
| 2.0 - 4.0 | 27 (15.2) | 35 (19.3) | |
| 4.1 - 5.9 | 44 (24.7) | 47 (26.0) | |
| ≥ 6 | 88 (49.4) | 86 (47.5) | |
| Pneumonia (from medical history) | | | 0.909 |
| Yes | 55 (30.9) | 54 (29.8) | |
| Nosocomial pneumonia (from chest radiograph or medical history) | | | 0.706 |
| Yes | 16 (9.0) | 14 (7.7) | |

Adapted from sponsor's electronic submission CO3 p. 53

Note: Additional risk factors include all risk factors for UGI bleeding in addition to mechanical ventilation. The presence of pneumonia at Baseline was identified at Screening from the patient medical history. Nosocomial pneumonia was diagnosed by a chest radiograph performed on Day 1 prior to the

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administration of trial drug or determined from patient medical history. The denominator for calculating percentages was the number of ITT patients in each treatment group.

* Based on the Fisher's Exact test (pH, pneumonia, nosocomial pneumonia) and the t-test (APACHE II Score, ISS).

Medical Officer Comments: The percentage of patients with additional two risk factors was higher in the cimetidine group compared to OSB-IR (35% vs. 31%), however; the percentage of patients with three or more risk factors was higher for the OSB-IR group compared with the cimetidine group (69% vs. 64%). The percentages of patients with acute renal failure, coagulopathy, and sepsis were at least 5-6% higher at baseline in the OSB-IR group compared with the cimetidine group. The OSB-IR group had a higher baseline mean APACHE II score than the cimetidine group (24.7 vs 22.7).

The percentage of patients with a pH of <2.0 was higher in the OSB-IR group compared to the cimetidine group (10.1 vs 6.6%); the reverse is true for the percentage of patients with a pH between 2.0-4.0 (cimetidine=19.3% vs OSB-IR=15.2%). A total of 34 OSB-IR and 39 cimetidine patients were taking H₂RA treatment at Screening.

Prior and concomitant medications were as expected for the critically ill patients enrolled in this trial.

More than 80% of both the OSB-IR and cimetidine patients were dosed according to the protocol dosing instructions.

Efficacy Results and Tabulations of Individual Patient Data

Primary Efficacy Endpoint

The primary efficacy endpoint for this trial was the occurrence of clinically significant UGI bleeding. The numbers and percentages of patients with clinically significant UGI bleeding in the PP and ITT analysis populations are summarized in the table below.

Table 7A: Number (%) of Patients with Clinically Significant UGI Bleeding by Analysis Population

| Analysis Population | OSB-IR n (%) (N = 157) | Cimetidine n (%) (N = 146) | Difference in Bleeding Rates (%) | Confidence Interval for the Difference in Bleeding Rates (%) | P-value* |
|-----------------------|------------------------------|----------------------------------|--|--|----------|
| Per-Protocol (PP) | 7 (4.5) | 10 (6.8) | -2.4 | (-100.0, 2.8) | 0.003 |
| Intent-to-Treat (ITT) | 7 (3.9) (N = 178) | 10 (5.5) (N = 181) | -1.6 | (-100.0, 2.8) | 0.002 |

Adapted from sponsor's electronic submission Trial CO1 p 55

Note: A non-inferiority analysis was used to compare the rates of UGI bleeding in each treatment group, by

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constructing a one-sided $\alpha=0.025$ confidence interval for the difference in bleeding rates between OSB-IR and cimetidine. The difference in bleeding rates was calculated as OSB-IR - cimetidine. Since the upper bound of this confidence interval is less than 5%, it is concluded that OSB-IR is not inferior to cimetidine in the prevention of UGI bleeding. The denominator for calculating percentages was the number of ITT or PP patients in each treatment group.

* Based on the normal approximation z-test.

In the analysis of both the PP and ITT populations, OSB-IR was not inferior to cimetidine, since the upper boundary of the confidence interval for the difference in bleeding rates was less than 5%.

A superiority analysis of the primary endpoint for patients in the OSB-IR group compared with cimetidine group showed no statistically significant difference ($p=0.238$) between groups.

In addition to the 17 patients who met the primary endpoint, there were 3 patients who were withdrawn from the trial because of active UGI bleeding and one patient who was transferred to another hospital while actively bleeding. Three of these patients were in the cimetidine group and one was in the OSB-IR group. Inclusion of these 4 patients with the 17 patients who met the primary endpoint does not alter the result of the superiority analysis, but does provide additional support for the non-inferiority conclusion.

Characteristics of Clinically Significant Upper Gastrointestinal Bleeding

Examination of the characteristics of clinically significant UGI bleeding in this trial focused on the following issues:

- The day on which clinically significant UGI bleeding occurred
- The site of UGI bleeding
- Blood products administered to patients with clinically significant UGI bleeding
- Predictive value of baseline risk factors
- Effects of enteral feeding and inadequate pH control

The Day on which Clinically Significant UGI Bleeding Occurred

Although there is a general perception that PPIs are slower to achieve control of gastric pH ($pH>4$) than H₂RAs, the omeprazole immediate-release (OSB-IR) suspension administered to critically ill patients in the C03 trial clearly raised gastric pH more quickly than IV cimetidine. To better evaluate the clinical outcome (prevention of UGI bleeding) during the early treatment period, the day when clinically significant UGI bleeding occurred was examined by treatment group.

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Table 8A: Number (%) of Patients with Clinically Significant Bleeding by Trial Day Bleeding Occurred

| Trial Day Bleeding Occurred | OSB-IR (N=7) n (%) | Cimetidine (N=10) n (%) |
|-----------------------------|--------------------------|-------------------------------|
| 1 | 1 (14.3) | 2 (20.0) |
| 2 | 0 (0.0) | 2 (20.0) |
| 3 - 7 | 4 (57.1) | 4 (40.0) |
| ≥ 8 | 2 (28.6) | 2 (20.0) |

Adapted from sponsor's electronic submission Trial CO3 p 57

In the first two days of treatment with trial drugs, one OSB-IR-treated patient and four cimetidine-treated patients developed bleeding.

The Site of UGI Bleeding

Endoscopies were not required in this trial, however, the sponsor provided a CRF page for recording the endoscopy for any patient who met the primary endpoint. An endoscopy was recorded on the CRF for only one patient in the cimetidine group where bleeding was present. Upper endoscopy confirmed that the site of bleeding was in the stomach, with erosions noted in the stomach and duodenum.

Blood Products Administered to Patients with Clinically Significant UGI Bleeding

Blood products were administered to 4 of 7 OSB-IR-treated patients (57.1%) and 5 of 10 cimetidine-treated patients (50.0%) patients who bled.

Predictive Value of Baseline pH and Other Baseline Risk Factors

With respect to the two baseline characteristics, number of risk factors and baseline gastric pH levels, patients who bled did not appear to be different than the entire population of all patients under study.

Table 9A: Mean APACHE II Score at Baseline for Patients with Clinically Significant Upper GI Bleeding

| OSB-IR (n=7) | | Cimetidine (n=10) | |
|-----------------|-----|----------------------|-----|
| Mean | SD | Mean | SD |
| 27.3 | 6.6 | 24.0 | 7.3 |

Adapted from sponsor's electronic submission Trial CO3 p 58

Note: Means and standard deviations (SD) were based on the number of patients with clinically significant bleeding in each treatment group.

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The mean APACHE II score for patients with clinically significant bleeding in the OSB-IR group was higher than that for patients with clinically significant bleeding in the cimetidine group (27.3 vs. 24).

Effects of Enteral Feeding and Inadequate pH Control

Because early enteral feeding may prevent or confound the detection of UGI bleeding and inadequate pH control may predispose patients to UGI bleeding, these parameters were examined (see table below).

Table 10A: Relevant Clinical Parameters for Patients with Clinically Significant UGI Bleeding

| | OSB-IR (n=7) | | Cimetidine (n=10) | |
|--|-----------------|------|----------------------|------|
| | n | % | n | % |
| Patients bleeding prior to feeding | 2 | 28.6 | 7 | 70.0 |
| Patients bleeding after feeding began | 5 | 71.4 | 3 | 30.0 |
| Patients with inadequate pH control in the 24 hours prior to bleeding* | 0 | 0.0 | 2 | 20.0 |

Adapted from sponsor's electronic submission Trial CO3 p 59

More cimetidine-treated patients had bleeding prior to feeding compared with patients treated with OSB-IR, reflecting that bleeding tended to occur earlier in cimetidine-treated patients.

Inadequate pH control was defined as two consecutive pH measurements ≤ 4 at least 1 hour apart on the same day. All OSB-IR-treated patients (7) and 80% (8) of cimetidine-treated patients with clinically significant UGI bleeding had adequate pH control in the 24 hours prior to the start of bleeding.

Upper Gastrointestinal Bleeding Not Meeting the Primary Endpoint

The number and percentage of patients with UGI bleeding that did not meet the primary efficacy endpoint are presented in the next table.

Table 11A: Number (%) of Patients With UGI Bleeding That Did Not Meeting the Primary Endpoint

| Bleeding | OSB-IR (N=178) | Cimetidine (N=181) | P-value* |
|--|-------------------|-----------------------|----------|
| | n (%) | n (%) | |
| UGI bleeding that did not meet primary efficacy endpoint | 27 (15.2) | 48 (26.5) | 0.0094 |
| Discontinued while actively bleeding | 1 (0.6) | 3 (1.7) | |

Adapted from sponsor's electronic submission Trial CO3 p 60

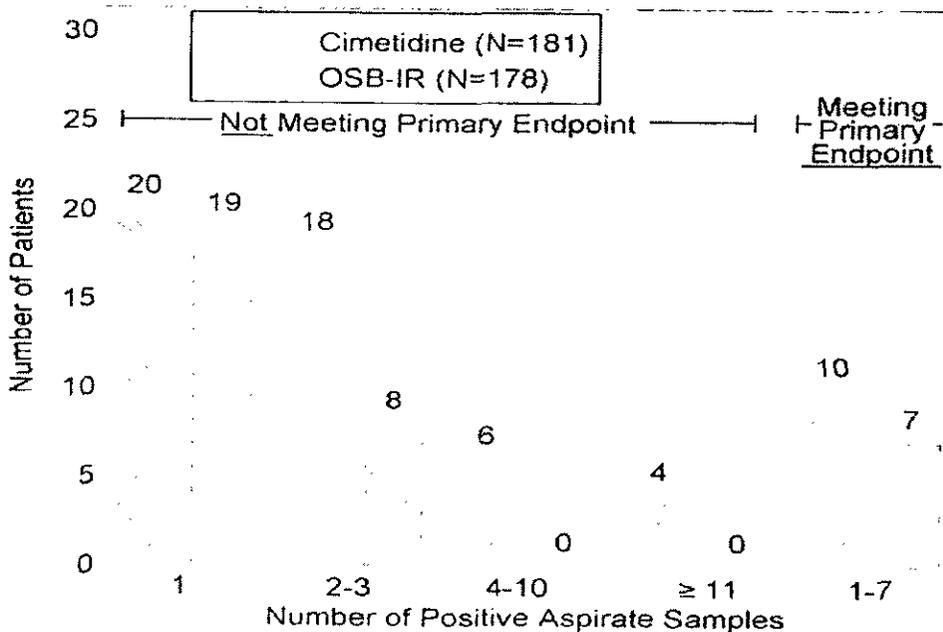
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Three patients with active bleeding in the cimetidine group were discontinued from the trial by the investigators; two of these patients (Patients 02121 and 09404) were discontinued due to specific concerns by the investigators about the UGI bleeding, and the third patient (Patient 17108) was transferred to an intensive care unit at another hospital while actively bleeding. This latter patient was transferred 1 hour and 5 minutes after the start of an active bleed that did not clear with 100 mL of room temperature normal saline lavage. In the OSB-IR group of patients, there was one patient (Patient 60581) who was also discontinued by the investigator for UGI bleeding that did not meet the efficacy endpoint.

The number of gastric aspirate samples with either bright red blood or Gastrocult-positive coffee ground material for patients not meeting the primary efficacy endpoint are presented in the figure below.

Figure 2A: Number of Patients With Positive Gastric Aspirate



Note: A positive gastric aspirate is a gastric aspirate sample that indicated the presence of bright red blood or coffee ground material. Positive gastric aspirates could have occurred on any trial day.

There was a statistically significant difference ($p=0.009$) between treatment groups with regard to the number of patients who had at least one gastric aspirate sample positive for either bright red blood or Gastrocult-positive coffee ground material that did not meet the criteria for clinically significant UGI bleeding. Among the patients not meeting the primary endpoint, 48 patients in the cimetidine group and 27 patients in the OSB-IR group had at least one gastric aspirate sample that was positive for UGI bleeding during the trial.

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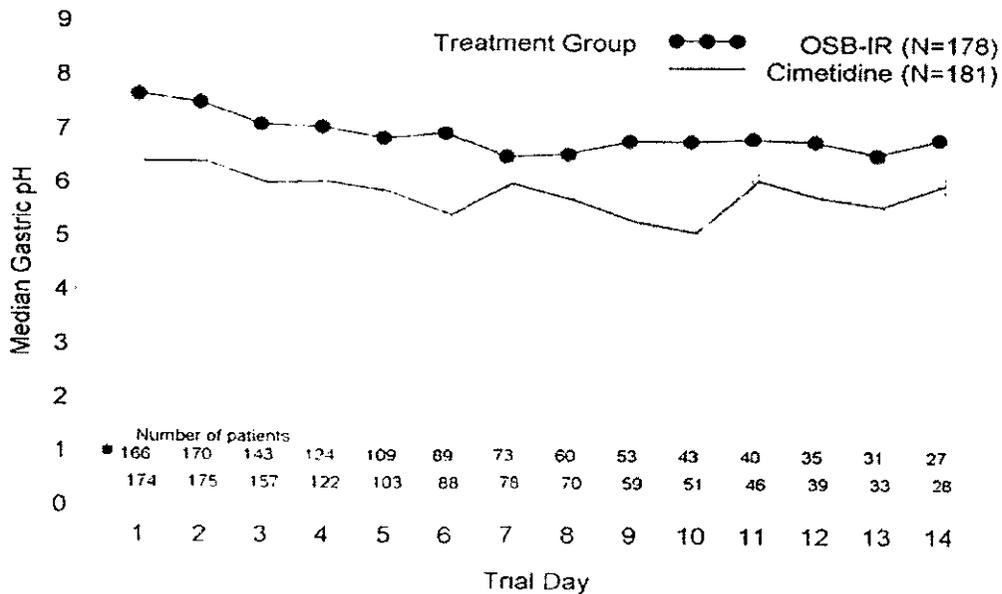
There also was a statistically significant difference ($p=0.033$) between the two treatment groups with regard to the number of positive gastric aspirate samples per patient. Among the patients not meeting the primary endpoint, none of the OSB-IR treated patients had more than three positive gastric aspirate samples. Eight of the OSB-IR treated patients had two to three positive gastric aspirate samples, compared with 18 of the cimetidine patients. The mean number of positive gastric aspirate samples was 3.4 samples/patient who bled (161 positive gastric aspirate samples for 48 patients) in the cimetidine group and 1.3 samples/patient who bled (36 positive gastric aspirate samples for 27 patients) in the OSB-IR group.

Secondary Efficacy Assessments

Median Gastric pH Values

The median and 25th and 75th percentiles of gastric pH are presented for each trial day in the next figure.

Figure 3A: Median Gastric pH by Trial Day



Note: The median gastric pH was first calculated for each patient for each trial day. The median and the 25th and 75th percentiles of these by-patient medians were tabulated by trial day. The curves have been offset to avoid overlap of the percentile bars. Predose pH measurements on Day 1 were excluded from the median calculation.

Median gastric pH values in the OSB-IR group were significantly higher on each of the 14 trial days compared with those in the cimetidine group ($p<0.001$ for each day of Day 1 through Day 13, $p=0.008$ for Day 14).

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Median gastric pH values in the OSB-IR group were significantly higher on each of the 14 trial days compared with those in the cimetidine group. The variability in median daily gastric pH values (as shown by the width of the 25th and 75th percentile bars in the above figure) was less in the OSB-IR group on each of the 14 trial days compared with the cimetidine group. After Day 8, at least 25% of the cimetidine-treated patients had a median gastric pH < 4.

For both treatment groups, approximately 40% of the patients were treated with PPIs or H₂RAs in the 24 hours prior to trial entry. The acid suppressant drugs may have contributed to the high baseline gastric pH for some patients. Other factors, including the severity of the patient's overall condition, appear to have contributed as well.

The median gastric pH in the OSB-IR and cimetidine groups was similar prior to the first dose of oral trial drug ($p=0.460$), OSB-IR-treated patients had significantly higher pH during the entire first two days of treatment ($p<0.001$ for all comparisons).

Median gastric pH in OSB-IR treated patients was higher than the median gastric pH in cimetidine-treated patients for patients in all strata and at all time points after the initiation of dosing.

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Table 12A: Median Predose and Postdose Gastric pH on Day 1 and Day 2 by Pretreatment Gastric pH

| | Pretreatment Gastric pH | Median Gastric pH | | | | | |
|------------|-------------------------|-------------------|--------------------|----|-----------------------|----------|--|
| | | OSB-IR (N=178) | | | Cimetidine (N=181) | | |
| | | n | Median (25th,75th) | n | Median (25th,75th) | P-value* | |
| Predose 1 | < 2.0 | 21 | 1.4 (1.0,1.7) | 15 | 1.3 (1.2,1.6) | 1.000 | |
| | 2.0 - 4.0 | 25 | 2.9 (2.2,3.5) | 37 | 3.0 (2.3,3.5) | 0.801 | |
| | 4.1 - 5.9 | 41 | 5.0 (4.4,5.5) | 38 | 5.1 (4.5,5.5) | 0.783 | |
| | > 6 | 90 | 7.1 (6.7,7.8) | 87 | 7.0 (6.6,7.4) | 0.142 | |
| Postdose 1 | < 2.0 | 20 | 7.6 (7.0,8.1) | 12 | 5.2 (2.6,6.4) | <0.001 | |
| | 2.0 - 4.0 | 22 | 7.9 (7.3,8.1) | 33 | 4.2 (3.5,5.4) | <0.001 | |
| | 4.1 - 5.9 | 36 | 7.7 (7.1,8.2) | 36 | 5.6 (4.7,6.4) | <0.001 | |
| | ≥ 6 | 86 | 8.1 (7.4,8.4) | 79 | 6.9 (6.4,7.2) | <0.001 | |
| Predose 2 | < 2.0 | 19 | 7.0 (3.1,7.9) | 14 | 5.8 (3.6,6.4) | 0.423 | |
| | 2.0 - 4.0 | 22 | 7.2 (6.6,7.6) | 34 | 5.7 (4.0,7.0) | 0.008 | |
| | 4.1 - 5.9 | 37 | 7.4 (7.0,7.9) | 35 | 5.6 (4.5,6.6) | <0.001 | |
| | > 6 | 84 | 7.6 (7.1,8.3) | 82 | 7.0 (6.5,7.4) | <0.001 | |
| Postdose 2 | < 2.0 | 18 | 7.8 (7.6,8.3) | 13 | 5.8 (4.8,6.8) | <0.001 | |
| | 2.0 - 4.0 | 20 | 7.9 (7.6,8.5) | 32 | 5.8 (4.5,7.0) | <0.001 | |
| | 4.1 - 5.9 | 37 | 8.1 (7.4,8.5) | 33 | 5.1 (4.3,6.7) | <0.001 | |
| | > 6 | 78 | 8.1 (7.6,8.3) | 68 | 6.9 (6.3,7.3) | <0.001 | |
| Predose 3 | < 2.0 | 19 | 7.3 (5.7,8.3) | 13 | 5.4 (2.4,6.7) | 0.011 | |
| | 2.0 - 4.0 | 22 | 7.5 (6.5,7.9) | 35 | 6.1 (4.1,7.1) | 0.007 | |
| | 4.1 - 5.9 | 40 | 7.2 (5.5,8.2) | 35 | 6.1 (4.1,7.2) | 0.008 | |
| | ≥ 6 | 85 | 7.5 (6.6,8.2) | 85 | 6.8 (6.2,7.3) | <0.001 | |
| Postdose 3 | < 2.0 | 17 | 7.7 (7.3,8.1) | 11 | 5.0 (3.8,6.7) | 0.001 | |
| | 2.0 - 4.0 | 21 | 7.6 (7.1,8.1) | 31 | 5.6 (4.4,6.6) | <0.001 | |
| | 4.1 - 5.9 | 36 | 8.0 (7.5,8.6) | 32 | 5.7 (3.6,6.7) | <0.001 | |
| | ≥ 6 | 75 | 7.9 (7.5,8.4) | 72 | 6.9 (6.2,7.2) | <0.001 | |

Adapted from sponsor's electronic submission Trial CO3 p 66

Note: Pretreatment gastric pH: the last pH prior to the first administration of oral trial drug. The median and the 25th and 75th percentiles were tabulated for each aspirate. Dose 2 was administered 6-8 hours after Dose 1. Dose 1 and Dose 2 are considered the loading dose regimen. Postdose aspirates were collected 1 to 2.5 hours after NG/OG administration of trial drug.

* Wilcoxon Rank-Sum Test.

Median gastric pH values were significantly ($p < 0.001$) higher for the OSB-IR group compared with those for the cimetidine group on Day 1 and Day 2 of the trial.

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Table 13A: Median Gastric pH by Trial Day

| Trial Day | OSB-IR | | Cimetidine | | P-Value* |
|------------------|--------|---|------------|---|----------|
| | Median | 25 th and 75 th percentiles | Median | 25 th and 75 th percentiles | |
| Day 1 | 7.7 | 7.2, 8.2 | 6.4 | 5.1, 7.1 | <0.001 |
| Day 2 | 7.5 | 7.0, 8.0 | 6.4 | 5.4, 7.1 | <0.001 |
| Pre-dose | | | | | |
| Day 1 | 6.0 | 4.0, 7.1 | 5.9 | 3.7, 7.0 | 0.460 |
| Day 2 | 7.4 | 6.4, 8.2 | 6.7 | 5.0, 7.2 | <0.001 |
| Days 3 - 7 | 6.5 | 5.4, 7.1 | 5.9 | 4.5, 6.7 | 0.005 |
| Days ≥ 8 | 6.2 | 5.0, 6.8 | 6.1 | 4.1, 6.6 | 0.182 |
| Post-dose | | | | | |
| Day 1 | 7.8 | 7.3, 8.3 | 6.4 | 4.8, 7.1 | <0.001 |
| Day 2 | 7.9 | 7.4, 8.4 | 6.4 | 5.1, 7.1 | <0.001 |
| Days 3 - 7 | 8.0 | 7.5, 8.2 | 5.5 | 4.5, 6.5 | <0.001 |
| Days ≥ 8 | 7.8 | 7.3, 8.2 | 5.5 | 4.1, 6.5 | <0.001 |

Adapted from sponsor's electronic submission Trial CO3 p 67

Note: The predose gastric pH for Day 1 is the last pH measurement taken prior to the first dose of oral trial drug on Day 1. The predose gastric pH for Day 2 is the last pH measurement taken prior to the third dose of oral trial drug. The postdose gastric pH for Day 1 is the pH measurement taken two hours after the first dose of oral trial drug on Day 1. The postdose gastric pH for Day 2 is the pH measurement taken two hours after the third dose of oral trial drug on Day 2. For Day 3-Day 14, the predose gastric pH is the last gastric pH measurement taken prior to the administration by NG/OG tube of the oral trial drug and the postdose gastric pH is the gastric pH measurement taken one hour after the administration of oral trial drug.

* Based on the Wilcoxon Rank Sum test.

Median gastric pH values were significantly ($p < 0.001$) higher for the OSB-IR group compared with those for the cimetidine group on Day 1 and Day 2 of the trial.

Predose pH values:

On Day 2 and for the Day 3 through Day 7 interval, the median predose gastric pH values for the OSB-IR group were > 6 and were significantly higher compared with the cimetidine group ($p < 0.001$ and $p = 0.005$, respectively). For rest of the 14-day trial (Days ≥ 8), the median predose gastric pH values for the OSB-IR group were > 6 and were similar to those for the cimetidine group. This indicated that OSB-IR sustained adequate pH control until the next dose administration at least as well as cimetidine (Table 13A).

Postdose pH values:

The postdose median pH values for the OSB-IR patients were significantly ($p < 0.001$) higher than those for the cimetidine patients throughout the trial (including Day 1, Day 2, the Day 3 through Day 7 interval, and Days > 8).

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The percentage of patients with median gastric pH values > 4 on Day 1 and Day 2 are presented in the next table.

Table 13A: Percent of Patients with a Median Gastric pH > 4 on Day 1 and Day 2

| Trial Day | OSB-IR | | Cimetidine | | P-Value* |
|-----------|--------|--------|------------|--------|----------|
| | n | (%) | n | (%) | |
| Day 1 | 162 | (97.6) | 154 | (88.5) | 0.001 |
| Day 2 | 169 | (99.4) | 157 | (89.7) | <0.001 |

Adapted from sponsor's electronic submission Trial CO3 p 68

Note: The median gastric pH was calculated for each patient for Day 1 and Day 2, and the percent of patients with a median gastric pH > 4 on Day 1 and Day 2 was compared by treatment group. The denominator for calculating percentages was the number of ITT patients with at least one pH measurement on indicated trial day in each treatment group.

* Based on the Fisher's Exact test.

A significantly higher percentage of patients in the OSB-IR group had median gastric pH values > 4 on both Day 1 (p=0.001) and Day 2 (p<0.001).

Maintenance of Gastric pH > 4

One of the objectives of this trial was to show that OSB-IR maintained gastric pH > 4 throughout the 14-day trial. Control of gastric pH was considered inadequate if the gastric pH was ≤ 4 for measurements of two consecutive gastric aspirates, at least 1 hour apart on the same day. This definition of adequate control triggered directions for increasing the dose of the both oral and IV trial drug.

The number and percentage of patients with at least one occurrence of two consecutive pH measurements ≤ 4 are presented in the next table.

Table 14A: Inadequate pH Control

| | OSB-IR (N=178) | | Cimetidine (N=181) | | P-value* |
|--|-------------------|--------|-----------------------|--------|----------|
| | n | (%) | n | (%) | |
| Number of patients with two consecutive aspirates with pH ≤ 4 | | | | | |
| One episode | 25 | (14.0) | 53 | (29.3) | <0.001 |
| More than one episode | 7 | (3.9) | 52 | (28.7) | <0.001 |
| One or more episodes | 32 | (18.0) | 105 | (58.0) | <0.001 |
| Number of patients receiving at least one dose increase | 26 | (14.6) | 95 | (52.5) | <0.001 |

Adapted from sponsor's electronic submission Trial CO3 p 69

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Note: Failure to maintain adequate pH control was defined as two consecutive gastric aspirates with pH ≤ 4 at least one hour apart on the same day. The denominator for calculating percentages was the number of ITT patients in each treatment group.

More patients in the cimetidine group had one or more pH measurements ≤ 4 during the trial compared with patients in the OSB-IR group needing for more dose adjustments.

The table below presents the number and percentage of patients with a median gastric pH > 4 on Day 3 and ≤ 4 on the last day of pH measurements.

Table 15A: Loss of Adequate pH Control

| | OSB-IR (N=123) n (%) | Cimetidine (N=102) n (%) | P-value* |
|--|----------------------------|--------------------------------|----------|
| Median pH > 4 on Day 3 and ≤ 4 on the day of last pH measurements | 8 (6.5) | 23 (22.5) | <0.001 |

Adapted from sponsor's electronic submission Trial CO3 p 69

Note: Patients included in this table had adequate pH control on Day 3 (median daily pH > 4) and a median pH ≤ 4 for the last day on which measurements were available.

* Based on the Fisher's Exact test.

There were significantly more more cimetidine-treated patients compared with OSB-IR-treated patients (22.5% versus 6.5%, respectively; $p < 0.001$) who had a pH with a median pH > 4 on day 3 and \leq on the day of last pH measurements.

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Extent of Exposure

Table 16A: Duration of Trial Drug Exposure

| Number of Days Exposed to Trial Drug | OSB-IR | Cimetidine |
|--------------------------------------|-------------|-------------|
| | (N=178) | (N=181) |
| | n (%) | n (%) |
| 1 | 11 (6.2) | 4 (2.2) |
| 2 | 24 (13.5) | 16 (8.8) |
| 3 | 19 (10.7) | 34 (18.8) |
| 4 | 16 (9.0) | 22 (12.2) |
| 5 | 18 (10.1) | 11 (6.1) |
| 6 | 16 (9.0) | 12 (6.6) |
| 7 | 13 (7.3) | 7 (3.9) |
| 8 | 8 (4.5) | 13 (7.2) |
| 9 | 8 (4.5) | 9 (5.0) |
| 10 | 6 (3.4) | 6 (3.3) |
| 11 | 4 (2.2) | 4 (2.2) |
| 12 | 4 (2.2) | 6 (3.3) |
| 13 | 5 (2.8) | 5 (2.8) |
| 14 | 26 (14.6) | 32 (17.7) |
| Mean | 6.60 | 7.05 |
| S.D. | 4.26 | 4.35 |

Adapted from sponsor's electronic submission Trial CO3 p 72

Note: The number of days exposed to trial drug was calculated as the number of days from the day of first drug administration to the day of last drug administration. The denominator for calculating percentages was the number of ITT patients in each treatment group.

The table above shows that approximately 50% of patients in both the OSB-IR and cimetidine treatment groups were still being treated with trial drug by Day 6, with approximately 15% of the patients in both groups still in the trial on Day 14. The mean days of drug exposure is 6.6 for OSB-IR and 7 for I.V. cimetidine .

Adverse Events

It was expected for this critically ill population that most of the patients in both groups will have one AE; 82.0% of OSB-IR and 80.7% of cimetidine patients.

In the OSB-IR C03 trial, during the treatment period, there were a total of 48 deaths; OSB-IR=27, cimetidine=21. During the post-trial follow-up period (2 to 30 days after the last day of trial drug administration), there were 43 deaths (OSB-IR=25, cimetidine=18). None of the deaths were considered by the investigators to be related to a trial drug. Deaths in the OSB-IR group during the trial and 30 days post-trial dose were numerically increased but not statistically significant. It is to be noted that the percentage of patients with ≥ 3 risk factors for UGI bleeding at baseline was slightly higher for the OSB-IR group compared with the

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cimetidine group (69.1% vs. 64.6%). Patients in the OSB-IR group have a more serious baseline disease characteristics when compared to the cimetidine group. The percentages of patients with acute renal failure, coagulopathy, and sepsis were at least 5%-6% higher at baseline in the OSB-IR group compared to the cimetidine group. Moreover, the mean APACHE II score (a prognostic factor for mortality) for patients in the OSB-IR group at baseline was significantly higher than that for patients in the cimetidine group (24.7 versus 22.7, respectively; $p=0.010$). Patients who died in the OSB-IR group had a mean APACHE II score of 28 at baseline compared to 24.2 in the cimetidine group, which puts the OSB-IR group at higher risk for mortality (~55% vs. ~40%).¹⁰

A total of 81 patients experienced at least one SAE (OSB-IR=44, cimetidine=37) excluding nosocomial pneumonia and clinically significant UGI bleeding; these SAEs were considered not related to OSB-IR and were all anticipated given the serious underlying disease in these patients. When nosocomial pneumonia and clinically significant UGI bleeding were included, a total of 115 patients experienced at least one SAE (OSB-IR=61 and cimetidine=54). From 2 to 30 days after the last day of trial drug administration, 17 patients in the OSB-IR group and 16 patients in the cimetidine group experienced an SAE.

Nosocomial Pneumonia

A total of 37 patients, 20 in the OSB-IR group and 17 in the cimetidine group, were diagnosed with nosocomial pneumonia, a protocol designated SAE, during this trial. The pneumonia in 12 of these patients (6 in each treatment group) was diagnosed within the first 3 days (≤ 72 hours) of the start of trial drug administration and may therefore have been related to pretreatment conditions. If nosocomial pneumonia events are combined with all other respiratory events, the incidence of respiratory AEs was 31.5% in the OSB-IR group and 35.9% in the cimetidine group.

Upper GI Bleeding

A total of 17 patients with clinically significant UGI bleeding were considered by the sponsor to have an SAE. Two additional patients had UGI bleeding that was reported as an SAE after being discontinued from the trial.

- Patient 31192 (OSB-IR group) developed hematemesis and melena three weeks after stopping the trial drug. The patient became hypotensive, with a hemoglobin of 6.3 g/dL, and was treated with blood transfusions and norepinephrine. An upper endoscopy revealed a large gastric ulcer that was treated with cautery and local injections of epinephrine. Following the upper endoscopy, esomeperazole was started.
- Patient 32251 (cimetidine group) was extubated and withdrawn from the trial. Three days later, the patient developed gastric bleeding and required transfusion of two units of packed red blood cells and four units of fresh frozen plasma. The

¹⁰ National Center for Emergency Medicine Informatics: APACHE II Score Interpretation

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available documentation indicated that the patient did not receive any other treatment.

The following are AEs with an incidence of $\geq 10\%$ in the OSB-IR and cimetidine groups: thrombocytopenia (10.1% and 6.1%, respectively), pyrexia (20.2% and 16.0%), hyperglycemia NOS (10.7% and 11.6%), hypokalemia (12.4% and 13.3%), and hypomagnesemia (10.1% and 9.9%).

The frequently reported AEs reflect the seriousness of the underlying medical conditions of this patient population. The higher level of sepsis at baseline in the OSB-IR group compared to the cimetidine group (34.8% vs. 28.7%) may explain the higher incidence of thrombocytopenia (10.1% vs. 6.1%) and pyrexia (20.2% vs. 16.0%) in the OSB-IR-treated patients. At baseline, there were 7 patients in the OSB-IR who had thrombocytopenia and 5 patients in the cimetidine group.

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Table 17A: Number (%) of Patients with Adverse Events by Body System

| MedDRA Body System | OSB-IR (N=178) | | Cimetidine (N=181) | |
|--|-------------------|------------------------------|-----------------------|------------------------------|
| | All AEs n (%) | Drug Related AEs n (%) | All AEs n (%) | Drug Related AEs n (%) |
| OVERALL (Number of patients with at least one AE or one drug-related AE) | 146 (82.0) | 5 (2.8) | 146 (80.7) | 10 (5.5) |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | 38 (21.3) | 1 (0.6) | 32 (17.7) | 4 (2.2) |
| CARDIAC DISORDERS | 55 (30.9) | 0 (0.0) | 46 (25.4) | 0 (0.0) |
| CONGENITAL, FAMILIAL AND GENETIC DISORDERS | 1 (0.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ENDOCRINE DISORDERS | 3 (1.7) | 0 (0.0) | 8 (4.4) | 0 (0.0) |
| EYE DISORDERS | 5 (2.8) | 0 (0.0) | 9 (5.0) | 0 (0.0) |
| GASTROINTESTINAL DISORDERS * | 39 (21.9) | 1 (0.6) | 42 (23.2) | 2 (1.1) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 51 (28.7) | 1 (0.6) | 49 (27.1) | 0 (0.0) |
| HEPATOBIILIARY DISORDERS | 5 (2.8) | 0 (0.0) | 5 (2.8) | 0 (0.0) |
| IMMUNE SYSTEM DISORDERS | 1 (0.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| INFECTIIONS AND INFESTATIONS | 58 (32.6) | 0 (0.0) | 43 (23.8) | 0 (0.0) |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | 17 (9.6) | 0 (0.0) | 12 (6.6) | 0 (0.0) |
| INVESTIGATIONS | 19 (10.7) | 0 (0.0) | 25 (13.8) | 1 (0.6) |
| METABOLISM AND NUTRITION DISORDERS | 72 (40.4) | 0 (0.0) | 81 (44.8) | 0 (0.0) |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | 6 (3.4) | 0 (0.0) | 5 (2.8) | 0 (0.0) |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) | 1 (0.6) | 0 (0.0) | 1 (0.6) | 0 (0.0) |
| NERVOUS SYSTEM DISORDERS | 22 (12.4) | 0 (0.0) | 21 (11.6) | 0 (0.0) |
| PSYCHIATRIC DISORDERS | 12 (6.7) | 0 (0.0) | 25 (13.8) | 1 (0.6) |
| RENAL AND URINARY DISORDERS | 11 (6.2) | 0 (0.0) | 18 (9.9) | 0 (0.0) |
| REPRODUCTIVE SYSTEM AND BREAST DISORDERS | 2 (1.1) | 0 (0.0) | 5 (2.8) | 0 (0.0) |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS † | 42 (23.6) | 0 (0.0) | 51 (28.2) | 0 (0.0) |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | 22 (12.4) | 2 (1.1) | 21 (11.6) | 2 (1.1) |
| SURGICAL AND MEDICAL PROCEDURES | 5 (2.8) | 0 (0.0) | 4 (2.2) | 0 (0.0) |
| VASCULAR DISORDERS | 36 (20.2) | 1 (0.6) | 23 (12.7) | 0 (0.0) |

Adapted from sponsor's electronic submission Trial CO3 p.76

Note: The denominator for calculating percentages was the number of ITT patients in each treatment group. Relationship to trial drug was defined as follows: AEs determined by the Investigator to have either a possible or probable relationship to trial drug are only considered as drug related if the Investigator correctly attributed the AE to the trial drug actually received (ie, AEs attributed to the trial drug not received are not considered as drug related). For multiple occurrences of same AE with different relationships to trial drug (related and not related) the AE was tabulated as related. Body systems were coded using MedDRA Version 5.0.

* Clinically significant UGI bleeding was considered an SAE but it is not included in this table. It is presented separately in Table 11.4.1-1.

† Nosocomial pneumonia was considered an SAE but it is not included in this table. It is presented separately in Table 12.3.3-1.

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Based on the investigator's assessment: Refer to table 18A.

Drug-related AEs were reported for 5 patients treated with cimetidine:

- nausea (1),
- vomiting (1),
- thrombocytopenia (1),
- hypotension (1),
- rash (2), and
- pyrexia (1).

All these AEs are included in the current Prilosec® labeling except for hypotension.

Drug-related AEs were reported for 10 patients treated with cimetidine:

- pruritus (1),
- rash (2),
- increased bilirubin (1),
- abnormal liver enzymes (1),
- diarrhea (1),
- vomiting (1),
- restlessness (1), and
- thrombocytopenia (4).

There were no clinically meaningful differences between the two treatment groups in the number of patients with AEs by body system.

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Table 18A: Number (%) of Patients with Frequently Occurring Adverse Events (experienced by $\geq 3\%$ of patients) by Body System and Preferred Term

| MedDRA Body System Preferred Term | OSB-IR (N=178) | | Cimetidine (N=181) | |
|---|-------------------|------------------------------|-----------------------|------------------------------|
| | All AEs n (%) | Drug Related AEs n (%) | All AEs n (%) | Drug Related AEs n (%) |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | | | | |
| Anaemia NOS | 14 (7.9) | 0 (0.0) | 14 (7.7) | 0 (0.0) |
| Anaemia NOS Aggravated | 4 (2.2) | 0 (0.0) | 7 (3.9) | 0 (0.0) |
| Thrombocytopenia | 18 (10.1) | 1 (0.6) | 11 (6.1) | 4 (2.2) |
| CARDIAC DISORDERS | | | | |
| Atrial Fibrillation | 11 (6.2) | 0 (0.0) | 7 (3.9) | 0 (0.0) |
| Bradycardia NOS | 7 (3.9) | 0 (0.0) | 5 (2.8) | 0 (0.0) |
| Tachycardia NOS | 6 (3.4) | 0 (0.0) | 6 (3.3) | 0 (0.0) |
| Ventricular Tachycardia | 8 (4.5) | 0 (0.0) | 6 (3.3) | 0 (0.0) |
| GASTROINTESTINAL DISORDERS | | | | |
| Constipation | 8 (4.5) | 0 (0.0) | 8 (4.4) | 0 (0.0) |
| Diarrhoea NOS | 7 (3.9) | 0 (0.0) | 15 (8.3) | 1 (0.6) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | | | |
| Hyperpyrexia | 8 (4.5) | 0 (0.0) | 3 (1.7) | 0 (0.0) |
| Oedema NOS | 5 (2.8) | 0 (0.0) | 11 (6.1) | 0 (0.0) |
| Pyrexia | 36 (20.2) | 1 (0.6) | 29 (16.0) | 0 (0.0) |
| INFECTIONS AND INFESTATIONS | | | | |
| Sepsis NOS | 9 (5.1) | 0 (0.0) | 9 (5.0) | 0 (0.0) |
| METABOLISM AND NUTRITION DISORDERS | | | | |
| Fluid Overload | 9 (5.1) | 0 (0.0) | 14 (7.7) | 0 (0.0) |
| Hyperglycaemia NOS | 19 (10.7) | 0 (0.0) | 21 (11.6) | 0 (0.0) |
| Hypernatraemia | 3 (1.7) | 0 (0.0) | 9 (5.0) | 0 (0.0) |
| Hypocalcaemia | 11 (6.2) | 0 (0.0) | 10 (5.5) | 0 (0.0) |
| Hypoglycaemia NOS | 6 (3.4) | 0 (0.0) | 8 (4.4) | 0 (0.0) |
| Hypokalaemia | 22 (12.4) | 0 (0.0) | 24 (13.3) | 0 (0.0) |
| Hypomagnesaemia | 18 (10.1) | 0 (0.0) | 18 (9.9) | 0 (0.0) |
| Hyponatraemia | 7 (3.9) | 0 (0.0) | 5 (2.8) | 0 (0.0) |
| Hypophosphataemia | 11 (6.2) | 0 (0.0) | 7 (3.9) | 0 (0.0) |
| PSYCHIATRIC DISORDERS | | | | |
| Agitation | 6 (3.4) | 0 (0.0) | 16 (8.8) | 0 (0.0) |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS † | | | | |
| Acute Respiratory Distress Syndrome | 6 (3.4) | 0 (0.0) | 7 (3.9) | 0 (0.0) |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | | | | |
| Decubitus Ulcer | 6 (3.4) | 0 (0.0) | 5 (2.8) | 0 (0.0) |
| Rash NOS | 10 (5.6) | 2 (1.1) | 11 (6.1) | 2 (1.1) |
| VASCULAR DISORDERS | | | | |
| Hypertension NOS | 14 (7.9) | 0 (0.0) | 6 (3.3) | 0 (0.0) |
| Hypotension NOS | 17 (9.6) | 1 (0.6) | 12 (6.6) | 0 (0.0) |

Adapted from sponsor's electronic submission Trial CO3 p 78

Note: Adverse events tabulated were those that occurred in $\geq 3\%$ of all patients. The denominator for calculating percentages was the number of ITT patients in each treatment group. Relationship to trial drug was defined as follows: AEs determined by the Investigator to have either a possible or probable relationship to trial drug were only considered as drug related if the Investigator correctly attributed the AE to the trial drug actually received (ie, AEs attributed to the trial drug not received were not considered as

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drug related). For multiple occurrences of the same AE with different relationships to trial drug (related and not related), the AE was tabulated as related. Body systems and preferred terms were coded using MedDRA Version 5.0.

* Clinically significant UGI bleeding was considered an SAE but it is not included in this table. It is presented separately in Table 11.4.1-1.

† Nosocomial pneumonia was considered an SAE but it is not included in this table. It is presented separately in Table 12.3.3-1.

Deaths

Table 19A: Number (%) of Patients Who Died and Cause of Death (SAE) by Body System

| MedDRA Body System | OSB-IR (n=178) N (%) | Cimetidine (n=181) N (%) |
|---|----------------------------|--------------------------------|
| OVERALL (Number of patients who died) | 27 (15.2) | 21 (11.6) |
| CARDIAC DISORDERS | 9 (5.1) | 5 (2.8) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 1 (0.6) | 2 (1.1) |
| INFECTIONS AND INFESTATIONS | 5 (2.8) | 6 (3.3) |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | 2 (1.1) | 1 (0.6) |
| METABOLISM AND NUTRITION DISORDERS | 0 (0.0) | 1 (0.6) |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) | 1 (0.6) | 0 (0.0) |
| NERVOUS SYSTEM DISORDERS | 9 (5.1) | 7 (3.9) |
| RENAL AND URINARY DISORDERS | 0 (0.0) | 1 (0.6) |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | 2 (1.1) | 3 (1.7) |

Adapted from sponsor's electronic submission Trial C03 p 79

Note: The number and percent of patients in each treatment group reporting at least one occurrence of an SAE that resulted in death up to 1 day after the last dose of oral trial drug administration was tabulated by body system. The denominator for calculating percentages was the number of ITT patients in each treatment group. Body systems were coded using MedDRA Version 5.0. No SAE that resulted in death was considered related to trial drug.

There were more patients in the OSB-IR group compared to the cimetidine group (27 vs. 21) who died during the trial (up to one day after the last day of trial drug administration). In the post-trial follow-up period (2 to 30 days after the last day of trial), there were 43 deaths (25 in the OSB-IR and 18 in the cimetidine group).

Three patients who had nosocomial pneumonia which developed after 3 days of trial drug administration died during the trial (2 patients in the OSB-IR group and 1 patient in the cimetidine group). These patients are included in Table 19A. The cause of death for any of these patients was not nosocomial pneumonia. The patient treated with OSB-IR died with intracranial hypertension and stroke/myocardial infarction. The cimetidine-treated patient was given respiratory arrest (NOS) as the cause of death. Four additional patients developed nosocomial pneumonia after 3 days of trial drug administration and died 2 to

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30 days after the last day of trial drug administration (1 OSB-IR-treated patient and 3 cimetidine-treated patients).

Serious Adverse Events

The number of patients with SAEs is presented in the next table by body system and relationship to trial drug as assessed by the investigators. Primary endpoint UGI bleeding and nosocomial pneumonia are not included in this table.

Table 20A: Number (%) of Patients with Serious Adverse Events by Body System

| MedDRA Body System | OSB-IR (N=178) | | Cimetidine (N=181) | |
|--|-------------------|-------------------------------|-----------------------|-------------------------------|
| | All SAEs n (%) | Drug Related SAEs n (%) | All SAEs n (%) | Drug Related SAEs n (%) |
| OVERALL (Number of patients with at least one SAE or one drug-related SAE) | 44 (24.7) | 0 (0.0) | 37 (20.4) | 0 (0.0) |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | 3 (1.7) | 0 (0.0) | 2 (1.1) | 0 (0.0) |
| CARDIAC DISORDERS | 15 (8.4) | 0 (0.0) | 7 (3.9) | 0 (0.0) |
| GASTROINTESTINAL DISORDERS * | 3 (1.7) | 0 (0.0) | 2 (1.1) | 0 (0.0) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 2 (1.1) | 0 (0.0) | 3 (1.7) | 0 (0.0) |
| HEPATOBIILIARY DISORDERS | 1 (0.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| INFECTIONS AND INFESTATIONS | 7 (3.9) | 0 (0.0) | 11 (6.1) | 0 (0.0) |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | 3 (1.7) | 0 (0.0) | 2 (1.1) | 0 (0.0) |
| INVESTIGATIONS | 1 (0.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| METABOLISM AND NUTRITION DISORDERS | 0 (0.0) | 0 (0.0) | 1 (0.6) | 0 (0.0) |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) | 1 (0.6) | 0 (0.0) | 1 (0.6) | 0 (0.0) |
| NERVOUS SYSTEM DISORDERS | 11 (6.2) | 0 (0.0) | 8 (4.4) | 0 (0.0) |
| RENAL AND URINARY DISORDERS | 2 (1.1) | 0 (0.0) | 1 (0.6) | 0 (0.0) |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS † | 3 (1.7) | 0 (0.0) | 9 (5.0) | 0 (0.0) |
| VASCULAR DISORDERS | 1 (0.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

Adapted from sponsor's electronic submission Trial CO3 p 80

Note: The number and percent of patients in each treatment group reporting at least one occurrence of an SAE or one occurrence of a drug related SAE for each body system up to 1 day after the last day of oral trial drug administration were tabulated. The denominator for calculating percentages was the number of ITT patients in each treatment group. Relationship to trial drug was defined as follows: SAEs determined by the Investigator to have either a possible or probable relationship to trial drug were only considered as drug related if the Investigator correctly attributed the SAE to the trial drug actually received (ie, SAEs attributed to the trial drug not received were not considered as drug related). For

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multiple occurrences of same SAE with different relationships to trial drug (drug related and not drug related) the SAE was considered drug related. Body systems were coded using MedDRA Version 5.0.

* Clinically significant UGI bleeding was considered an SAE but it is not included in this table. It is presented separately in Table 11.4.1-1. † Nosocomial pneumonia was considered an SAE but it is not included in this table. It is presented separately in Table 12.3.3-1.

The percentage of patients with at least one SAE was slightly higher in the OSB-IR compared to the cimetidine group (24.7% vs. 20.4%), table 20A. When both nosocomial pneumonia and clinically significant UGI bleeding are included, the overall number of patients with SAEs is 115 (32.0%), including 61 patients in the OSB-IR group and 54 patients in the cimetidine group. There were no reports of SAEs related to trial drug.

Nosocomial Pneumonia

All cases of nosocomial pneumonia were considered SAEs.

Table 21A: Number (%) of Patients Diagnosed with Nosocomial Pneumonia

| Nosocomial Pneumonia | OSB-IR (N=178) n (%) | Cimetidine (N=181) n (%) | P-Value* |
|---|----------------------------|--------------------------------|----------|
| Diagnosed at baseline | 16 (9.0) | 14 (7.7) | 0.706 |
| Nosocomial pneumonia confirmed on or before Day 3 | 6 (3.4) | 6 (3.3) | 1.000 |
| Nosocomial pneumonia confirmed after Day 3 ** | 14 (7.9) | 11 (6.1) | 0.540 |

Adapted from sponsor's electronic submission Trial CO3 p 82

Note: The denominator for calculating percentages was the number of ITT patients in each treatment group.

* Based on the Fisher's Exact test.

** An exit chest radiograph was to be obtained within 48 hours after trial drug was stopped. If a patient developed signs or symptoms of pneumonia after their exit chest radiograph was done, additional chest radiographs were to be obtained.

Nosocomial pneumonia occurring on or before Trial Day 3 (≤ 72 hours of the start of trial drug administration) is considered likely to have been related to conditions that existed prior to the start of trial drug. Therefore, patients with confirmation of nosocomial pneumonia during this time period (6 patients in each group) are summarized separately from those patients whose nosocomial pneumonia was more likely to be related to conditions after the start of trial drug (14 in the OSB-IR group and 11 in the cimetidine group). Nine patients with nosocomial pneumonia died during the trial and follow-up period; nosocomial pneumonia was not given as the cause of death for any of these patients.

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Clinical Laboratory Evaluations

Normal Laboratory Values at Baseline

Approximately 80% to 90% of patients in the OSB-IR and cimetidine groups had normal oxygenation at Baseline, with the percentage increased somewhat at Termination. Serum sodium and potassium were normal in approximately 90% to 98% of patients in both the OSB-IR and cimetidine group at baseline and termination.

Abnormally Low Laboratory Test Values at Baseline

Approximately 50% of patients in the OSB-IR and cimetidine groups had abnormally low arterial pH at Baseline, and approximately 75% of patients in both groups showed normal arterial pH at Termination.

Hematocrit was abnormally low in 30% to 40% of patients in the OSB-IR and cimetidine groups at Baseline and Termination.

Abnormally High Laboratory Test Values at Baseline

WBC count was abnormally high in approximately 40% of patients in the OSB-IR and cimetidine groups at Baseline. At Termination, the percentage of patients with abnormally high white blood cell counts was somewhat lower in both groups. Serum creatinine was abnormally high in 30% to 40% of patients in the OSB-IR and cimetidine groups at Baseline and Termination.

Vital Signs, Physical Findings, and Other Observations Related to Safety

Normal Vital Signs at Baseline

Approximately 75% to 92% of patients in both the OSB-IR and cimetidine treatment groups had normal temperatures at Baseline and Termination.

Respiratory rates for most patients in both the OSB-IR and cimetidine groups were normal at Baseline (with ventilatory support) and normal at Termination when the patients were stable enough to permit withdrawal of ventilatory support.

Abnormally Low Vital Signs at Baseline

Mean arterial pressure was abnormally low in approximately 55% of patients in both the OSB-IR and cimetidine group at Baseline and was approximately 30% at Termination.

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Abnormally High Vital Signs at Baseline

About 60% of patients in the OSB-IR and cimetidine groups had abnormally high heart rates at Baseline and decreased to about 40% at Termination.

Pharmacokinetic and Pharmacodynamic Evaluations

No pharmacokinetic analyses were performed. Pharmacodynamic evaluations (gastric pH) were made as supportive, secondary efficacy assessments.

Conclusions

The results from OSB-IRC03 have shown that OSB-IR was not inferior to continuous IV cimetidine with respect to the prevention of clinically significant bleeding in both PP and ITT populations, with 10 patients (PP=6.8%) in the cimetidine treatment group and 7 patients (PP=4.5%) in the OSB-IR treatment group meeting the primary endpoint.

In addition to the 17 patients who met the primary endpoint for clinically significant bleeding, 2 patients in the cimetidine group and 1 patient in the OSB-IR group were withdrawn from the trial by the investigator because of clinically meaningful UGI bleeding. In the cimetidine group, an additional patient was actively bleeding and was transferred to another hospital before the endpoint requirements were met. Significantly fewer OSB-IR- treated patients (34 patients [19.1%]) were found to have had at least one gastric aspirate containing blood compared to cimetidine-treated patients (58 patients [32%]), $p=0.005$. Of the 15 patients who had 4 or more positive aspirates, only 3 were in the OSB-IR treatment group. These results provide supportive evidence of the finding of the non-inferiority of OSB-IR to cimetidine in preventing UGI bleeding in critically ill patients.

In addition, the median daily gastric pH in the OSB-IR group was significantly higher than median daily gastric pH in the cimetidine group for each of the 14 days of the study, and fewer patients in the OSB-IR group required dose increases to keep the gastric pH above 4 (14.6% vs. 52.5%). The variability in median daily gastric pH was less in the OSB-IR than in the cimetidine group. It is believed that maintaining gastric pH above 4 decreases the potential for UGI bleeding and prevent progression of mucosal damage.

The safety experience in the trial (including deaths) reflected the severity of the underlying medical conditions of these critically ill patients. Most of the patients in both the OSB-IR and cimetidine groups had at least one AE. The distribution across body systems for AEs related to trial medication was similar for the OSB-IR and cimetidine groups.

None of the deaths were considered by the investigators to be related to a trial drug. Deaths in the OSB-IR group during the trial and 30 days post-trial dose were numerically increased but not statistically significant. It is to be noted that the percentage of patients with ≥ 3 risk factors for UGI bleeding at baseline was slightly higher for the OSB-IR group compared with

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the cimetidine group (69.1% vs. 64.6%). Patients in the OSB-IR group have a more serious baseline disease characteristics when compared to the cimetidine group. The percentages of patients with acute renal failure, coagulopathy, and sepsis were at least 5%-6% higher at baseline in the OSB-IR group compared to the cimetidine group. Moreover, the mean APACHE II score (a prognostic factor for mortality) for patients in the OSB-IR group at baseline was significantly higher than that for patients in the cimetidine group (24.7 versus 22.7, respectively; $p=0.010$). Patients who died in the OSB-IR group had a mean APACHE II score of 28 at baseline compared to 24.2 in the cimetidine group, which puts the OSB-IR group at higher risk for mortality (~55% vs. ~40%).¹¹

The trial showed no evidence that administration of a daily dose of 40 mg increases the risk of developing nosocomial pneumonia in critically ill patients compared with a continuous IV infusion of cimetidine.

Vital signs and laboratory results were similar for the OSB-IR and cimetidine patient groups. All the trial drug-related OSB-IR AEs that were reported in this trial are consistent with the current Prilosec® labeling, with the exception of hypotension (reported for one patient).

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¹¹ National Center for Emergency Medicine Informatics (www.ncemi.org): APACHE II Score Interpretation

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APPENDIX C Recommendations for Labeling

The following are my recommendations for labeling changes:

1. In the "CLINICAL STUDIES" section, under subsection **C** **J** Upper Gastrointestinal Bleeding in Critically ill Patients", the following paragraph and bar graph should be deleted:

C

J

The above deletions should be replaced by the following paragraph:

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A double-blind, multicenter, randomized, non-inferiority clinical trial was conducted to compare Zegerid 40mg oral suspension and intravenous cimetidine for the [] of upper GI bleeding in critically ill patients (mean APACHE II score = 23.7). The primary endpoint was significant upper gastrointestinal bleeding defined as bright red blood which did not clear after adjustment of the nasogastric tube and a 5 to 10 minute lavage, or persistent Gastrocult® positive coffee grounds for 8 consecutive hours which did not clear with 100 cc lavage. Zegerid 40 mg (two doses administered 6 to 8 hours apart on the first day via orogastric or nasogastric tube, followed by 40 mg q.d. thereafter) was compared to continuous I.V. cimetidine (300 mg bolus, and 50 to 100 mg/hr continuously thereafter) for up to 14 days (mean=6.8 days). A total of 359 patients were studied, age range 16 to 91 (mean=55 yrs), 58.5% were males, and 64% were Caucasians. The results of the study showed that Zegerid was non-inferior to I.V. cimetidine, 10/181 — patients in the cimetidine group vs. 7/178 — patients in the — group experienced clinically significant UGI bleeding.

The sponsor conducted a non-inferiority study comparing Zegerid and cimetidine with a clearly defined primary efficacy endpoint of upper GI bleeding, therefore; the results of the study based on the primary efficacy endpoint should be described in this section, patients who did not meet the endpoint are only supportive of the study but not pivotal.

Demographic information should also be included in the description of the study.

The wording “reduction of risk” instead of [] of UGI bleeding is more appropriate to use in the label because it is more reflective of the design of the study.

2. In the “PRECAUTIONS” section, under subsection “General”, the following underlined text should be added to the paragraph.

Each 20mg and 40mg dose packet of ZEGERID™ contains 460 mg sodium in the form of sodium bicarbonate. This should be taken into consideration for patients on a sodium restricted diet.

Each 20mg and 40mg dose packet of ZEGERID™ contains 1680 mg (20 mEq) of sodium bicarbonate. Sodium bicarbonate is contraindicated in patients with metabolic alkalosis and hypocalcemia. Sodium bicarbonate should be used with caution in patients with Bartter's syndrome, hypokalemia, and respiratory alkalosis, and problems with acid-base balance. Long term administration of bicarbonate with calcium or milk can cause milk alkali syndrome.

The above information was added to inform clinicians and patients that both dose packets contains the same amount of sodium and sodium bicarbonate. If a patient is given two packets of 20mg a day, then that patient receives twice as much sodium

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and sodium bicarbonate for that day. In addition, since this formulation will be indicated in critically ill patients in the intensive care unit, clinicians should be cautious when using this medication in patients who have problems with acid-base balance.

3. In the "PRECAUTIONS" section, under subsection "Information for Patients" the following paragraph should be modified with additions in underlined text and deletions in strikethrough:

ZEGERID™ is supplied as ~~...~~
] powder for oral suspension (40 mg or 20 mg). It should be taken on an empty stomach at least one hour prior to a meal. ~~...~~
] Zegerid is available as 20mg and 40mg single dose packet

Directions for use: ~~...~~ Empty packet contents ~~...~~ into a small cup containing ~~...~~ 1-2 tablespoons ~~...~~ of water. ~~...~~] DO NOT USE OTHER LIQUIDS OR FOODS. Stir well and drink immediately. Refill cup with water and drink.

This modifications are recommended to make the 40mg dose label consistent with the 20mg dose label of Zegerid.

4. In the "ADVERSE REACTIONS" section, the underlined text should be added to the following paragraph to replace the Drug-Related AEs column that was deleted in the Critically-ill Adverse Events Table :

A controlled clinical trial conducted in 359 critically ill patients, comparing ZEGERID™ 40 mg once daily to I.V. cimetidine 1200 mg/day for up to 14 days, demonstrated that the adverse event profile for ZEGERID™ was similar to that of I.V. cimetidine. The following AEs maybe related to OSB-IR: thrombocytopenia, rash, pyrexia, hypotension and nosocomial pneumonia.

This modifications will simplify the table of adverse events in critically ill patients by deleting the two columns of drug-related AEs and incorporating the information in the paragraph. Nosocomial pneumonia should also be included in this table of adverse events.

5. In the section "DOSAGE AND ADMINISTRATION", subsection ~~...~~] of **Upper Gastrointestinal Bleeding in Critically ill Patients**", the following paragraph should be modified:

The recommended adult oral dose of ZEGERID™ is 40mg initially followed by 40mg after 6 to 8 hours as a loading dose on the first day, then 40mg once daily. ~~...~~

]

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The wordings I recommended are much simpler and easier to understand.

6. The wording "reduction of risk" instead of \uparrow of UGI bleeding is more appropriate to use in the label because the former is more reflective of the design of the study.

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/s/

Lolita Lopez
11/12/04 03:50:02 PM
MEDICAL OFFICER

Ruyi He
11/12/04 04:00:52 PM
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